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PULMONARY EDEMA AND INFLAMMATION

An Analysis of Processes Involved in the Formation and Removal of Pulmonary Transudates and Exudates

BY

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THE NATHALIE GRAY BERNARD LECTURES DELIVERED AT THE BOWMAN GRAY SCHOOL OF MEDICINE, WAKE FOREST COLLEGE, WINSTON SALEM, NORTH CAROLINA, IN DECEMBER, 1944, TOGETHER WITH A FIFTH CHAPTER ON ARTIFICIAL RESPIRATION



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To

JAMES HOWARD MEANS

and

EUGENE FLOYD DUBOIS

with whom I have had the good fortune to work

idea—wine shop again—pen and ink—back again—cut and noble time, sir Sportsman, sir?" abruptly turning to Mr Winkl

Eventually the work was done and the lectures deliver returning to Boston, I decided to add a fifth chapter on a respiration, a subject of interest to me over many years and involved in many of the issues discussed in the sectior ceding it

It is quite true that I have been part of all the experi used in these lectures, but only part The first isolatior *quantitations of lung lymph flow were the accomplishm* Madeleine F Warren Later, Esther Hardenbergh and He Gilbert entered the discouraging task of right lymphatic cannulation and verification of the fact that the lymph co from this duct depended upon events in the lungs

It would be far short of reality if I failed to acknowled sagacity of our old associate, Louis Freni, in the important t selecting animals, and, through long experiments, vigilantly g ing their condition

Finally, to Katherine R Drinker, I ascribe textual acc and phrasing beyond my casual abilities

Cecil K Drinker, M

Harvard School of Public Health
January, 1945

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PULMONARY EDEMA AND INFLAMMATION

I

THE RELATION OF LUNG STRUCTURE TO EDEMA AND INFLAMMATION

THE SUBJECT of these lectures, pulmonary edema and inflammation, is a very old one, but since many people suffer and will continue to suffer from fluid in the lungs and in the pleural sacs physicians are inevitably interested in the conditions and processes involved in the appearance and removal of excessive pulmonary fluid

My interest in pulmonary edema and the events leading to it began twenty years ago when Churchill and I were engaged in experiments on the effects upon the amount of blood in the heart and lungs of graded obstruction of pulmonary arteries and veins, and other problems concerning the pulmonary circulation Day after day we speculated on the condition of the lungs at the end of the experiment Invariably there was atelectasis and pulmonary edema and I think even then we realized that almost any sort of analysis of the dynamics of what we saw at autopsy would be far more valuable than the measurements of pressures in the largest pulmonary blood vessels, which was our current objective This experience was that of all investigators of the problems of transudation and exudation in the lungs The experiment was finished when what had occurred was seen at autopsy, but there was no way to follow the development of the lesions

In 1942, Mrs Warren and I (1) found it relatively easy to collect lymph from the lungs of dogs by cannulating a large lymphatic in the anterior mediastinum This experiment was carried out under artificial respiration with the thorax open which of course destroyed the normal negative pressure in the chest Also, for reasons which will become clear later, the movements of the lungs during artificial respiration by means of a

positive blast of air delivered through a tracheal cannula are very different from those attending normal negative pressure breathing with the thorax unopened Not only are the movements of the lungs different, but positive pressure ventilation imposes very abnormal forces upon fluid in the alveoli and interstitial tissues of the lungs in the sense of moving such fluid into and along the lymphatics Yet, in spite of these unnatural conditions, it was possible, under constant artificial respiration, to gain a little information upon the production and movement of excessive fluid in the lungs The most interesting of our findings was the speed with which lack of oxygen in the ventilating air caused increased lymph flow, and the regularity with which this excessive lymph movement stopped when ventilation with pure oxygen relieved the asphyxia, provided the anoxia was relatively brief It was apparent that examinations of lymph flow from the lungs under natural conditions would have the possibility of giving a functional approach to the problem of pulmonary edema (2) We might, so it seemed, learn something of the progress of pulmonary transudation during its actual occurrence, rather than by reasoning after an experiment over the way in which pulmonary changes observed at autopsy had developed

When one labors for a long time upon investigations such as these, and gives an account of them afterwards, it often seems to his audience as if the investigator knew all of the conditions playing upon the experiments, was thoroughly aware of all the nuances in the progress of his work Such is never the case Much of what is learned from an experiment is learned as the worker ponders over it later, puts together odds and ends, and puzzles out the implications It is this sort of mental digestion of the experiments of many years which these lectures present

Structural Arrangements in the Lungs Significant in the Development of Pulmonary Edema

Capillaries —It is generally acknowledged that two factors are fundamental in causing abnormal transudation in the lungs and

pleural sacs They are, first, sustained increase in pulmonary capillary pressure and, second, anoxia It is not easy to apply experimentally either one of these causal factors of pulmonary edema alone Sooner or later the second factor begins to operate, and, clinically, while one or the other may be dominant in a particular case, they never, in my opinion, work alone Lack of oxygen causes increased permeability of blood capillaries all over the body In some tissues the endothelium is more resistant than in others Thus, one may completely occlude the circulation to the arm for some minutes without observing noticeable swelling when the tourniquet is released Resistance of the capillary endothelium in different tissues to oxygen lack is an interesting and immensely important phenomenon, since ordinarily the endothelium is considered to be a unit tissue, similar everywhere But structural similarity, so far as present microscopic observation permits, does *not mean functional identity In the possession of contractility*, for example, capillaries differ markedly in different regions, and, similarly, resistance to anoxia—an event so common as to be practically a physiological experience for all parts of the body—varies in the capillaries from tissue to tissue Methods for determining increased capillary permeability to water and dissolved substances are not sufficiently refined to permit grading the body tissues in regard to this property of endothelium but, in spite of lack of a precise estimate, we may consider, I believe, that the endothelium of lung capillaries is significantly assailable by anoxia The reason this fact is not more widely recognized clinically is not because anoxia will not cause prompt and steady leakage if it occurs, but is because of the difficulty of asphyxiating large groups of lung capillaries

With regard to capillary pressure as a factor in inducing abnormal filtration, it must be realized constantly that pressure inducing filtration through a membrane is directly related to the condition of the membrane at the moment Thus, the pressure in the lung capillaries of a patient with decompensated mitral stenosis and an inadequate right ventricle may be lower than normal nevertheless, anoxia may have so altered the endothelium of the

pulmonary capillaries as to render the low head of pressure disastrously effective in causing filtration of fluid into the alveolar interstitial tissue and into the alveoli

The arrangement of the lung capillaries is adapted beautifully to their function You gain an unforgettable picture of this adaptation if you deliver the lung of a pithed frog through the body wall inflate it slightly, and view the surface through the usual high dry lens of the microscope What you see in the simple, single sac lung of the frog is precisely what much more refined methods of observation disclose for the alveolar capillary circulation in the mammal Figure 1 is a reconstruction (magnified 480 times) of the capillary net in a mammalian alveolar wall (3) In visualizing this mesh, one should consider it overlaid on both sides by a delicate layer of alveolar epithelium It is the meat of a vital sandwich of which the enclosing outer layers are so tenuously thin as to be inconsequential in restraining diffusion of gas or of fluid from the capillaries The vascular area provided by this net is maximally great, and the fall in pressure between pulmonary arterioles and capillaries must be in proportion A glance at the circulated lung of the frog or mammal will show that blood rolls through this net in a sheet The lung does not possess capillary units of independent length of any consequence The capillary circulation in all the tissues of the body is netlike, not characterized by long independent channels as the words "capillary blood vessel" cause us to assume This arrangement provides an automatic safety valve against accessions of pressure, and nowhere is it so much in evidence as in the lung capillaries The lungs must meet the general bodily requirements for oxygen with astonishing speed It is not surprising, therefore, that they are organized to do this in a thoroughly passive way The evidence that lung capillaries are capable of adaptive independent contraction and relaxation to meet the needs of the moment is unconvincing If such reactions do occur in the sense implied by Wearn and his associates (4), investigators must have more substantial evidence of such reactions than experiments so far have supplied One can see that arteriolar constriction might alter the distribution of lung blood to a con

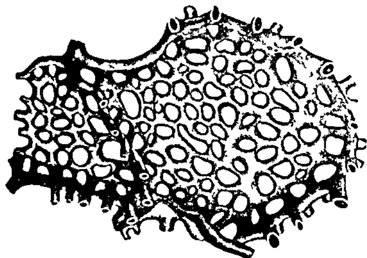


FIG 1—The capillary net in the wall of an alveolus × 480 (From Miller's *The Lung* 1937 fig 55 p 71 By permission of Charles C Thomas Publisher Springfield Illinois)



FIG 2—Plexus of lymphatics about the bronchi and pulmonary artery ×1 (From Miller by permission of the *American Review of Tuberculosis*, 1919 vol 3 fig 1 p 196 See also Miller (3) fig 66 p 88)

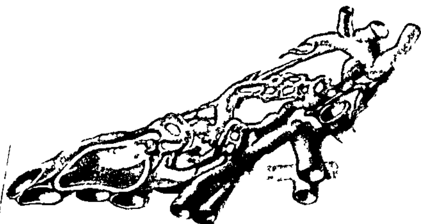


Fig 3 —Plexus of lymphatics about a pulmonary vein × 26 (From M
by permission of the *American Review of Tuberculosis* 1919 vol 3 fi
p 19 See also Miller (3) fig 67 p 90)



Fig 4 —Plexus of lymphatics in an interlobular septum × 16 (Fr
Miller by permission of the *American Review of Tuberculosis* 1919 vol
fig 4 p 200 See also Miller (3) fig 69 p 94)

siderable degree, but in a net, such as surrounds the alveoli, capillary reactions do not offer much in the way of regulating blood flow It has been estimated that the capillary area of the lungs available for gas exchange is about 140 sq m This huge surface, by virtue of the net arrangement of the capillaries, is very evenly available for the volume of blood thrown into it by each ventricular contraction The essential anatomical features of the pulmonary circulation are its perfect adequacy for taking all the blood that comes to it (4 l a minute at rest, 30 l a minute after a few seconds of hard physical work), and the freedom of anastomosis of its capillaries, making localized capillary blockage difficult And yet this very ability to meet maximal necessities poses subtle problems for us The fact that the lungs are much larger than is necessary to meet the resting needs of the body often allows functional disruption of much lung tissue to proceed for a long time with quiet persistence, but without striking apparent disablement—a fact which too often leads to unhappy eventuality Think of one of the commonest clinical experiences—a patient safely in bed with a moderate degree of cardiac decompensation There is little cause for alarm, a trifling dyspnea, slight cyanosis, and moderate edema of the lower part of the body Yet, so far as the lungs are con erned, this patient is getting oxygen through but a part of his ing tissue—a part which remains normal as other large sections lling with fluid go out of function Or recall how confidently the rgeon of today removes the lobe of a lung even an entire lung and the patient manages to carry on his respiratory functions well enough to live a reasonable sort of life He cannot shift suddenly into violent muscular effort, but he can be a relatively normal person if his physical activities are kept within bounds What Meltzer called his "margin of safety" is gone This is a fundamental conception for clinicians—the conception of the existence of protective mechanisms so beautifully ordered that doctors rarely realize how often they gamble upon safety margins We have an inherent confidence in the physical powers of patients, a confidence which time after time is justified because the human organism at rest operates so far below even average capacity A quantitative

justification of this confidence has been made for the lungs by Drastich and his collaborators (5) These investigators produced atelectasis and removed parts of the lungs in dogs, and, after their recovery, observed the animals during the moderate exercise of running on the level and during the more strenuous exercise of swimming They concluded that the dogs could run moderately and without embarrassment when 50 per cent of their lung tissue was actually gone Swimming a more strenuous exercise, caused the animals increasing difficulties The observers further secured evidence that when air was excluded from large amounts of lung tissue by blockage of a bronchus, although circulation through this unventilated tissue continued, the handicap for the animal was increased

There is a final peculiarity of the lung capillaries which is imposed by their position It is the fact that to very great degree the capillary endothelium in the alveoli depends for its oxygen supply on the alveolar air The pulmonary capillaries, unlike those in the rest of the body, do not dip into the general pool of oxygen brought by the arterial blood, but are dependent upon the conditions governing alveolar ventilation or, if surrounding blocked alveoli, to a large degree upon the precarious supply of oxygen remaining in the venous blood This is a matter to which further reference will be made later, but as a vital consequence of the anatomical position of the lung capillaries it requires mention at this time

Lymphatics—There is a very large literature upon the anatomy and pathology of the pulmonary lymphatic system, but there is comparatively little information upon the functional position of the widespread lymph vessels in the lungs Final draining trunks were cannulated in 1942, but with the chest open, satisfactory experiments in which lung lymph has been collected without thoracotomy are more recent

There are certain structural features of the pulmonary lymphatic system which appear to me of fundamental importance for understanding the accumulation and removal of excess fluid in the lungs Histological observations have shown that lymph capillaries

do not surround the alveoli Their ultimate saccular radicles end just short of the atria, around the alveolar ducts, and thus before the beginning of the largest quota of respiratory lung tissue This means that the alveolar septa must become turgescent with edema fluid before the lymphatics can be entered It is reasonable to feel that excess fluid filtered out of the lung capillaries can enter the alveolar air space just about as readily as it can spread inside the alveolar tissue toward the lymphatic capillaries at the atria Free alveolar fluid, invariably containing a certain amount of plasma protein, has, as far as removal is concerned, a fairly predictable destiny Such fluid may be removed through one or another of the following processes and routes (a) It may drift up through bronchioles and bronchi and eventually be coughed up (b) Proteins, water, and salts may be absorbed into the lung lymphatics and so travel slowly back to the blood (c) Protein may be broken down by enzymes and the smaller molecular nitrogenous compounds, with water and simple salts be absorbed into the alveolar capillaries

These alternatives pose consequences for the individual which are of great practical importance First, and easy to understand, is the fact that proteinized fluid in alveoli delivered slowly into bronchioles and on the way to possible expectoration is a potential blocker of air movement into the alveoli involved, and thus a means of causing local oxygen lack in families of lung capillaries With deprivation of oxygen supply, lung capillary endothelium will become more permeable to plasma water and solutes, and lung edema will inevitably become worse It is an outstanding feature of oxygen lack that wherever it occurs "anoxia begets anoxia" (6) in the lungs this is strikingly the case As I have pointed out the endothelium of pulmonary capillaries depends upon the alveolar air for oxygen supply It is thus the fact that the normal condition of the lung capillaries is directly related to the aeration of the alveoli which they surround If the normal ventilation of an alveolus is lacking the local supply of oxygen available to a lung capillary is perhaps little more than that remaining in the venous blood driven through the lungs by the

right ventricle If the individual involved is completely at rest, this venous oxygen may be of moment in maintaining a reasonably satisfactory environment for the endothelium of the lung capillaries, but if circumstances assure the return to the lungs of a venous blood practically desaturated as regards oxygen, the inevitable consequence is a progressive leakage of fluid from capillaries surrounding unventilated alveoli

The lymphatic vessels in the lung are both numerous and large It is impossible to give any figure for the volume of fluid these vessels may contain They are extremely distensible, and measures designed to cause lymph movement in them invariably result in immediate delivery of lymph After a time, however, lymph flow falls off unless conditions are simultaneously imposed which result in abnormal leakage of fluid from the blood in the lung capillaries It may seem remarkable that the lungs, which are organized so as to avoid excess fluid in their interstitial tissue, possess so large a lymphatic system Miller (3) has pointed out that the lungs are more extensively equipped with lymphatics than are the kidneys or liver It is a generalization in regard to the lymphatic system that lymph vessels are most numerous in the skin and in regions within the body which are in contact with the outside world The mucosa of the genito urinary tract, of the intestinal tract, and the surface and depths of the respiratory system are thus more heavily furnished with lymphatics than parts of the body isolated from the surface Lymphatics all over the body, to a greater degree than William Hunter (7) believed in 1784, are absorbing vessels which exist to remove proteinized fluid, bacteria, and foreign particles—in short, to remove every sort of material foreign to the tissues and unabsorbable by the blood vessels Figures 2, 3, and 4 from the many careful observations of Miller (3), suffice to show the extent of the lymphatic vascular system in the lungs

Judging from the position of the valves in the pulmonary lymphatics, the direction of flow of lung lymph is toward the hilum, where one finds the largest collections of pulmonary lymph nodes In this region one would expect to find radicles draining into the thoracic duct so that there should be the freest possible

movement of the lymph toward the great veins But, as a rule, no such arrangement exists Instead, all the lymph from the right and left lungs, except for a small area at the left apex, drains via the right lymphatic duct into the right subclavian vein The right duct, both in man and animals, is an exceedingly short and small vessel, and is thus a definite bottleneck at the end of a widespread system of lymphatic vessels In the dog, the right duct has been shown by Freeman (8) to have anastomotic connections with the thoracic duct in twelve out of twenty five carefully injected and examined animals Since the variable, small connecting radicles between the right and left sides are not effectively valved, lymph from either side may be directed into the other Obviously, connection between the thoracic duct and the right duct may be of great practical importance in the event of thoracic duct occlusion Also, it is the fact that cannulation of the thoracic duct in the expectation of collecting all the lymph from the intestinal tract may readily lead to grievous error We have often seen right duct lymph loaded with typical white chyle In spite of this confusing complication the facts are that in about 50 per cent of dogs, if the right lymphatic duct is cannulated, it is possible to collect the total output of lymph from the heart and lungs The right duct, it is true, receives small contributions from the liver and the right side of the thoracic cage, but in the quiescent, anesthetized dog the amount of lymph collected from the right duct expresses the lymph delivery from the contracting heart and the moving lungs If cardiac activity is kept reasonably constant, the quota of right duct lymph arising from the heart is constant, and variations in output reflect conditions in the lungs The anatomical problem of collecting lung lymph, as demonstrated by experiments in this laboratory, is illustrated in Figure 5, a diagrammatic representation of lung lymphatics in the dog These vessels in the dog are apparently very similar to those in man, with the exception that lymph nodes are much more plentiful in man—a fact true all over the body and for all animals

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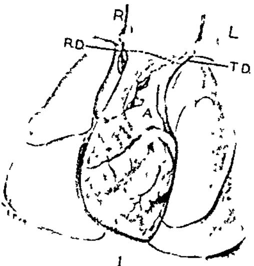
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assured the sources of lymph collected from the right lymphatic duct If one introduces 5 cc of 1 per cent T 1824 in *physiological* saline through a long glass catheter down the trachea into either the right or left lung, the dye will appear in a cannula previously placed in the right duct, but will not color thoracic duct lymph unless there is a very free communication between the right and left sides A further control of the amount of intercommunication is readily obtained by cannulating a lymphatic in either hind leg the cannula being directed centripetally, and injecting 10 cc of a finely divided suspension of graphite [1] This black suspension *will flow promptly into and from the thoracic duct into which a cannula* has been inserted, and if there is no communication with the right duct, lymph from it will remain clear On the other hand, if communication exists, black fluid will appear promptly in the right duct cannula The evidence for or against contamination of right duct lymph by thoracic duct lymph can be made even more emphatic if the thoracic duct is obstructed for a brief time when the black fluid first begins to flow from the cannula in it

The above discussion should make it clear that the collection of *lung lymph outside the chest is a trying task—so trying* it is in fact, that in spite of perfect exposure of the right lymphatic duct as it enters the subclavian vein collection can be accomplished successfully in only about 50 per cent of attempts This limitation of experimental possibilities depends wholly upon the anatomy of the lymphatics involved, and to it must be added the chances of failure dependent upon the technical difficulties of isolating and cannulating the right lymphatic duct To expose this duct, an incision is made over the lower 6 cm of the external

[1] Some years ago a graphite suspension *for intravital capillary injections* was described by Drinker and Church II (9) Graphite particles the visible pigment in this injection mass have the advantage of not being agglutinated by blood plasma [illegible] lymph nor do they adhere to the inner surface of vessels into which they are



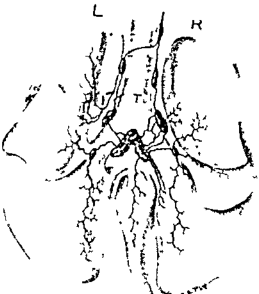


FIG 5.—Semidiagrammatic representation of the essential drainage paths for lung lymph in the dog *1*, anterior view The entrance of the right duct into the subclavian vein Cervical lymphatics *R* and *L* above the vein Broken lines indicate lymphatic vessels encountered fairly frequently *R D* right duct *T D* thoracic duct *2*, posterior view The typical arrangement of the lung lymphatics at the root of the lungs and a short distance above Broken line indicates a lymphatic seen occasionally and running into the thoracic duct *T*, trachea (Slightly modified from Warren Peterson and Drinker (2) fig 1 p 642)

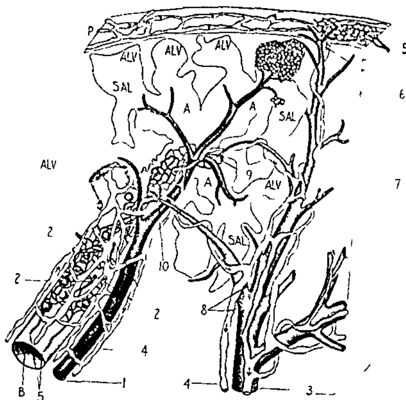


FIG 6 —General scheme of a primary lobule of a mammalian lung The subdivisions of the bronchial tree the pulmonary artery the pulmonary vein the lymphatics and the lymphoid tissue are shown

B *Bronchiolus respiratorius* which divides into two *ductuli alveolares* only one of which is carried out to its final subdivisions Alv *Alveoli* scattered along the bronchiolus respiratorius and the ductuli alveolares A A A Three *atria* two other atria connected with the ductulus are not indicated in the diagram S Al S Al *Sacculi alveolares* Alv Alv *Alveoli pulmonum* P *Pleura pulmonalis* 1 *Arteria pulmonalis* with its branches one of its terminal branches is carried out to show its breaking up into capillaries and how the arterial capillaries gradually pass over into venous capillaries which take part in the formation of a venous radicle 2 Branches of the arteria pulmonalis which are distributed to the *bronchiolus respiratorius* and *ductulus alveolaris* and then break up into capillaries which unite with capillaries derived from the *arteria bronchialis* to furnish the vascular supply to this portion of the bronchial tree 3 *Vena pulmonalis* with its branches of origin

jugular vein and straight over the thorax to the level of the third interspace The vein is dissected cleanly down to the junction with the subclavian vein, and all small branches must be tied with fine silk since it is imperative to keep the field bloodless and particularly to avoid small extravasations of blood between the fasciae of the neck The external jugular vein is next retracted outward, and, lying upon the fascia which floors the triangular space so exposed, the operator sees the main cervical lymphatic duct Around this duct a ligature is passed The duct, which is now followed down to the subclavian vein, leads either to the entrance or to the vicinity of the entrance of the right duct into the vein The duct itself is usually large enough to admit a pyrex cannula 1 mm in outside diameter, but it is well to have smaller sizes at hand, since the duct wall is delicate and the operator has little latitude for failure With the cannula tied in place and the dog breathing naturally, lymph flow begins at once and, if uncontaminated from the thoracic duct, will be steady but small in amount Milky lymph, obviously chyle coming from the right duct cannula, is sure evidence that lung lymph alone is not being secured, and the experiment is a failure If the lymph is clear and if pressure upon the abdomen, which is markedly effective in increasing lymph flow from the thoracic duct, does not accelerate flow from the right duct, the anatomical situation is apparently

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indicated at ... at the distal end of a

a capillary network which unites with the network of capillaries derived from branches of the arteria pulmonalis (2) to form the vascular supply of the final divisions of the bronchial tree 5 shows how in animals with a *thick* pleura the ... the formation of the capillary

favorable One can verify this impression still further by shifting from natural breathing to artificial respiration through a tracheal cannula This procedure will at once increase the delivery of lymph from the right duct, and reduces that from the left side If, at this stage of the experiment, it is desirable to be absolutely sure of the sources of the right duct lymph, the intrapulmonary and intralymphatic injections previously described may be made With experience, the operator will become able to leave these final injections until near the end of the experiment, and so save time and keep the pulmonary lymph free of T-1824 if chemical examinations are desirable

In summary, then

(a) If an operator learns how to cannulate the right lymphatic duct in the anesthetized dog and if he makes observations which show that during the period of his experiment cardiac activity is kept reasonably constant, he may conclude that his data upon changes in the amount of lymph and its protein content will reflect the amount of transudation and exudation that is occurring and will thus represent the progress of events in the alveoli and interstitial tissues of the lungs

(b) The varying competent controls or safeguards for ascertaining that the data obtained express the progress of events in the lungs alone have been described rather briefly but may be regarded as satisfactory

Alveoli —The surface for gas exchange provided by the lung alveoli in an adult is about 90 sq m This huge area, with the associated capillary net, is in reality a vast number of units It has been estimated that the total number of alveoli in man is 750 million, and that at rest but one twentieth of their total aerating surface is used

The main bronchus entering the lobe of a lung divides and sub divides until eventually cartilage disappears and the circular bronchioles with smooth muscle and elastic tissue in their walls are reached From the terminal bronchioles arise the respiratory bronchioles, and these divide into the alveolar ducts, each one of which forms the entrance into a lung lobule Figure 6, from

Miller (3), is a diagram[2] which shows the total architecture of a lobule A respiratory bronchiole, *B*, divides into two tubes—alveolar ducts—one cut off, the other leading into three atria, which, in turn, become the alveolar sacs and alveoli The bronchiole, not shown in the diagram, about 1 mm in diameter, is lined by ciliated columnar epithelium, with here and there a mucus-secreting goblet cell, and is well equipped with circular bands of smooth muscle, which upon contraction may entirely occlude the lumen of the tube Many elastic fibers, running in the main longitudinally, are found among the muscle bands and between the epithelial lining It is these fibers that stretch as the bronchiole lengthens during inspiration and return the tubes to a basic length in expiration When the respiratory bronchiole is reached, the epithelium becomes cuboidal and cilia disappear, as do goblet cells Here and there in the diagram the respiratory bronchiole is studded with button like projections the first alveoli which are encountered The cuboidal epithelium gives way to flattened cells as the tube is followed, and the many blood vessels just beneath the epithelium may here and there be so exposed to the surface as to provide for gas exchange It is significant that the bronchial artery supply of the air passages—arterialized blood from the left ventricle—ends at the beginning of the respiratory bronchiole, so that just as alveoli begin to appear the blood supply is venous via the pulmonary artery from the right ventricle While there are ordinarily no large connections between the systemic and pulmonary circulations, the capillaries of the two circuits anastomose freely

The bronchiolar bands of smooth muscle extend over the alveolar ducts to the atria and at each atrium form a miniature sphincter Elastic fibers, mainly longitudinal, are numerous in the alveolar ducts and pass on over the atria and alveoli From the atrial entrance onward, the epithelium becomes thin and platelike,

[2] I have chosen to follow Miller in the material which follows It may be that atria are artificial divisions of the respiratory part of the lobule as has been contended (Macklin 10) but so long as it is understood that they are cleancut parts of the alveolar respiratory structure no confusion need result.

and thus the alveoli contain nothing in their walls except blood capillaries and elastic and collagenous fibrils

In conclusion, certain points appear important for the issues met in disease

First, mucus-secreting cells become infrequent and disappear as the air passages near the respiratory part of the lungs are reached The utility of the mucus is apparently twofold It protects the upper surfaces of the respiratory tract against possible drying effects from the inspired air, and entraps particles of all sorts which impinge upon it Associated with regions of mucus production are cilia lashing upwards to assure the movement out of the lungs of foreign material trapped in the mucus

Second, the provision of so ample a supply of smooth muscle in the mammalian bronchioles and alveolar ducts, with the possibilities of complete contraction and relaxation, is structurally definite, but its purpose not easy to understand The autonomic innervation of this muscle, which permits complete relaxation by adrenin, is often taken advantage of in the treatment of asthmatic patients But smooth muscle possesses in highest degree the physiological quality called tone, and while one can recognize the usefulness of a tonic contractile state in arterioles containing blood under pressure, it is not so easy to understand the need for fairly extensive muscularization of the bronchioles, which are abundantly supplied with elastic fibers and through which air passes under no pressure requiring constraint In whales and porpoises, sphincteric muscles in the bronchioles apparently enable these animals to imprison air in the alveoli and to exert pressure upon it in the final phases of what amounts to expiration, so as to squeeze all possible oxygen out of the alveolar air But land mammals need no such economizing mechanism for their respiration Macklin (10), whose work upon the subject is of *fundamental significance*, has written a thorough review of his own and of other findings relative to smooth muscle in the lungs There can be no doubt of the widespread and plentiful distribution of smooth muscle from the trachea to the ends of the alveolar ducts, and it is also the fact that the amounts of muscle, as com

pared to other tissue, are greater in the finest divisions of the bronchi It is apparently certain that the bronchi and bronchioles both lengthen and widen during inspiration, and on expiration return to basic length and diameter When one considers that fairly deep breathing can occur at rates of fifty respirations per minute, it is obvious that if smooth muscle is to contract and relax in the positive manner ordinarily conceived for a muscular event, it must do so in active breathing so rapidly as to be in consistent with what is known of smooth muscle function To explain the variations in length and caliber which the air passages display in breathing, it seems to me essential to think of the smooth muscle as the tonic stabilizing effector in the mechanism, highly elastic, but endowed with the peculiar attribute of tone which enables it to operate effectively at different lengths, without at the same time interfering with the simple effects of the elastic fibers Smooth muscle, to my mind, is essentially the stabilizer of the air passages to the effective functional capacity of the moment This is why its distribution is so widespread At the same time—possibly as a relic of ancient heritage—the air passages also possess innervation of the smooth muscle and capacity for sudden out bursts of contraction and of relaxation, which, in the first case, are associated with spasmodic disease of the lungs and, in the second with the advantageous complete opening of the airway in times of stress I am aware that this analysis of the functions of the pul monary smooth muscle is not backed by specific observations It is merely my personal appraisal of a puzzling situation, and must be judged as worth just that and no more

Finally, it is of possible importance to note that the transition from air-conducting tubes to structures designed wholly for gas exchange occurs somewhat gradually, alveoli being present along the respiratory bronchioles and alveolar ducts It has been pointed out that lymphatic capillaries for absorption of foreign material are not found surrounding the true alveoli, and this is shown diagrammatically in Figure 6, but they are present in the tissue surrounding the first alveoli met by the ventilating air, and per haps make the clearance of exudates and transudates from the

alveoli somewhat more expeditious than from the larger respira tory part of the lobule

There is a problem concerning the ultimate construction of the pulmonary alveoli which has received a vast amount of clinical and experimental consideration No one questions the isolation of the several lobes of lungs Each lobe operates alone, without pos sibility of connection with other lobes in so far as ventilation is concerned The lobule has been pictured as the structurally isolated final unit of the lung This conception implies that aera tion of the lobule is accomplished through a single bronchiole and with obstruction of this tube no air can reach a particular group of alveoli I believe this conception is, in the main, true, but there are provisions which mitigate it

For more than a hundred years there has been a controversy as to whether the air passages in the lungs ended blindly, or whether some sort of communication between alveoli of different lobules existed so that complete deprivation of air entrance is not achieved unless a large bronchus is obstructed Loosli (11),[a] in 1937, made a careful search for the alveolar pores described by many earlier investigators Some workers, notably Miller (3), held that these minute communications between the alveoli of adjacent lobules could be found in pathological areas of lung tissue, but were absent in the normal lung Others declared them to be normal structures lined by extensions of alveolar epithelium Loosli found pores present in normal mammalian lungs when he examined thick sections after intra alveolar injections of homologous heparinized plasma This plasma clotted slowly in the living animal and its strands of fibrin constituted an injection mass traceable through the fine holes between alveoli Loosli was able to show that the pores were even more evident in the lungs of dogs and monkeys infected with pneumonia and killed at varying periods after the onset of the disease Figure 7 shows two illustrations from Loosli s paper Both are camera lucida drawings The first is a section

[a] The excellent paper by Loosli contains an interesting analysis of the literature upon alveolar pores and I therefore omit all save a few references upon this important subject

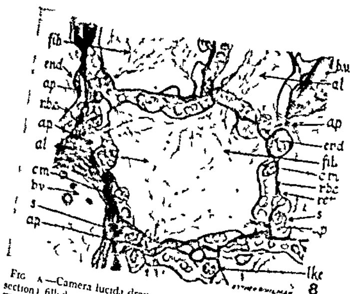


FIG A—Camera lucida drawing of a normal rat s lung (10 mi ron section) filled with heparinized plasma which was allowed to clot The alveoli are filled with a fibrin (fib) network and are connected by strands of fibrin through openings (a p) in the alveolar walls Microscopically the alveolar septums appear normal Mallory s azan technic Bausch and Lomb 2 mm objective and X 10 ocular Key to labels al alveolar space a p alveolar pore b v blood vessels c m capillary membrane end endothelial cell of capillary fib fibrin network lkc granular leukocyte r b c red blood cell r t reticulum s septal cell (From Loosli (11) fig 8 p 53 By permission of the American Medical Association Press

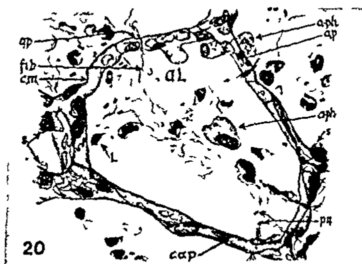


Fig 8 —Camera lucida drawing (made at two levels) of a thinly sectioned (10 microns) lung of a dog infected intratracheally with type I pneumococci and killed after two and a half hours The drawing represents the margin of a lesion in which the alveoli contained fibrin (*fib*) connected through pores (*a p*) in the alveolar walls and a few inflammatory exudate cells At this stage there is no desquamation of cells from the walls which have a normal appearance Hematoxylin eosin azure II Bausch and Lomb 2 mm objective and X 10 ocular camera lucida at stage level Key to labels *al* alveolar space *a p* alveolar pore *a ph* alveolar phagocyte *cap* blood capillary *c m* capillary membrane *fib* fibrin *L* lymphocyte *pn* pneumococcus *s* septal cell (From Loosli (11) fig 20 p 759 By permission of the American Medical Association Press)

from the lung of a normal rat, injected with heparinized rat plasma which was allowed to clot before the animal was killed The continuous strands of fibrin passing through alveolar pores are shown convincingly The second illustration shows the same sort of pores in the inflamed lung of a dog given experimental pneumonia Loosli s interest in the alveolar pores was concerned mainly with the possibility of the direct spread of infectious processes from one lobule to another, with eventual spread through an entire lobe To us, I believe, the possible significance of the pores extends into physiological factors involved in that most frequent of lung lesions, bronchiolar obstruction with a certain degree of atelectasis

Van Allen and his collaborators (12), in 1930, began a series of observations directed toward explaining the usefulness of the interalveolar communications Their papers, resulting from clinical observations and experimental work upon animals, deserve close attention They are an excellent example of the application of physiological thinking and research toward the clarification of clinical issues The point of view from which Van Allen's work stems is clearly expressed in the summary of one of his first papers (12 *d*)

> The principle of respiratory mechanics that has been described would appear to have a broad economic significance in the functioning of the lower respiratory tract Considering the exudative tendency of the bronchial mucosa and the disposition of the lungs to transudation,
>
> . . . .
>
> small as to be filled over considerable length by no more than a droplet of exudate or secretion, and the result of such occlusion would be completely to isolate the corresponding unit of respiratory ducts, atria, and alveoli If there were no peripheral interconnections Then, unless special expiratory effort were soon instituted to make use of the air available for expulsion, it would be lost by absorption Inspiration, no matter how forceful, would not be able to introduce air past the column of fluid to replace the absorbed air Atelectasis must soon develop and this lobule of parenchyma must then remain functionless until the exudate undergoes removal by absorption Under these circumstances

number of the actual pores is too great to deny them a major part in collateral respiration

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II

PHYSIOLOGICAL FACTORS IN PULMONARY EDEMA AND INFLAMMATION

IT IS NOW AGREED that rapid movements of water out of and into blood capillaries are dependent upon a balance of forces between the pressure of the blood in the capillaries and the osmotic attraction of water by the plasma proteins Figure 9 is a diagram contrasting the situations in the systemic and pulmonary circulations On the left, the systemic balance for normal water exchange is shown Blood is driven through a capillary under a pressure of 25 to 30 mm Hg The concentration of the plasma proteins is normally about 7 per cent, or a trifle less, and these proteins—most notably albumin—exert an osmotic pressure of 25 to 30 mm of water This relation is, in reality, a much less perfect balance of forces than it seems to be The figures in the diagram are correct for a capillary endothelial wall which is not permeable to the blood proteins, but it is well known today that under the ordinary conditions found in typical blood capillaries, such as those in the skin and subcutaneous tissues a small amount of blood protein leaks out steadily The fact is that normal blood capillaries all over the body possess an endothelial wall which, under the pressures ordinarily experienced, is just at the edge of fairly free protein leakage These lectures are not the place to return exhaustively to an old physiological problem, but I do want to point out that in any consideration of a balance of forces controlling water movement across a membrane, the membrane itself must never be forgotten, and, when the membrane is living, it may vary in permeability almost as rapidly as hydrostatic pressures change, and infinitely more rapidly than alterations occur in concentration of blood protein, upon which the colloid osmotic pressure depends

It is my belief—I cannot say conviction—that simple pulmonary edema and the more serious pulmonary exudations depend more upon alterations in the permeability of the lung capillaries than upon complicated pressure relations in the pulmonary circulation

Let us see what sort of case can be made for such a thesis Turn again to Figure 9 In the diagram on the right, the conditions for water movement into and out of the lung capillaries are reduced to

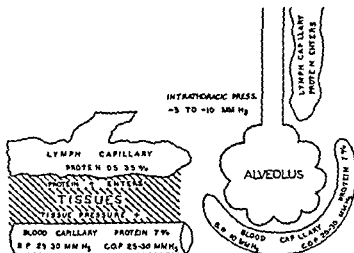


FIG 9—Diagrams of contrasting fundamental physiological relations between blood capillaries and tissues On the left a representation of typical relations in the skin on the right relations in the lungs

their simplest terms, and, in contrast to conditions in the systemic circuit, arresting facts are apparent The blood plasma traversing the lung capillary is necessarily identical in protein content and colloid osmotic pressure with that in the systemic circulation But the pulmonary capillary blood pressure is given as 10 mm Hg This is a guess based on indirect evidence, but is probably not far from the correct figure Opposing this is the colloid osmotic pressure of 25 to 30 mm Hg The arrangement would seem to assure dryness in the lung tissue, and since the alveolar capillaries are

separated from the air by the thinnest of barriers it is not surprising that the absorption of water from the alveoli may also be extremely rapid Colin (1), for example, found it possible to give 21 liters of water intratracheally to a horse in three and one-half hours, with no evidence of ill effects When a man has been submerged, it is not the water in the alveoli which makes the serious problem for his rescuers If the circulation is still in operation this water will be absorbed rapidly The endangering water is that in the bronchi and bronchioles This water forms a froth as it mixes with mucus, and becomes a means of excluding air, thus prolonging and intensifying the asphyxia against which those engaged in artificial respiration are struggling

In both clinical and experimental investigations of transudation and exudation in the lungs, the observer may concentrate upon abnormal pressures in the pulmonary circulation which he believes exist or which he has produced, but the degree to which localized pulmonary anoxia may also have had a share in causing the changes under observation can never be neglected Last March in a lecture (2 *a*) to the students and staff of the Children's Hospital in Boston, I attempted to discuss these problems, and now can perhaps go somewhat further Our concern is with three things first, the effects of anoxia on the caliber of capillaries and the permeability of their walls second, the possibilities for experiencing localized, persistent anoxia in the lungs, resulting in abnormal capillary leakage, and third, the pervasive character of the anoxic effects No one of these issues can be isolated entirely from the others

Anoxia, Capillary Dilatation, and Capillary Leakage in the Lungs—The broad problem of anoxia, capillary dilatation and capillary leakage in the lungs extends into the largest aspects of the regulation of the circulation Our preoccupation with the needs of the different mammalian tissues for oxygen has caused us to forget the fact that in all tissues there is, nearest to the blood stream and peculiarly important for oxygenation, the endothelium of the capillaries It is agreed that lack of oxygen causes capillaries to dilate wherever it occurs In the final sense, it has often been

held that the need for oxygen is the regulator of the circulation In a tissue such as muscle, it is easy to follow the idea that as metabolism increases, the capillary bed keeps pace with oxygen needs, through opening of temporarily closed vessels and widening of those conducting blood at the time muscular work began

Reactive hyperemia of this type occurs not only with ordinary functional activity but as a result of trauma of many sorts Since the vascular response to different stimuli is the same, it has been somewhat naively assumed that the final cause must be the same, and much time has been given to the search for some sort of chemical factor produced locally under a variety of initiating circumstances The most discussed of such compounds is histamine It has been an attractive hypothesis to consider that histamine, or a compound very like it, is formed in the tissues as a result of all sorts of trauma, and that this compound causes reactive hyperemia The effects of localized anoxia are conceived to be quite similar to trauma in bringing about the formation of this H substance from cells experiencing injury through oxygen lack There can be no doubt as to the utility of the localized changes in the circulation observed in a region of inflammation Through increase in the vascular bed, the injured tissue receives a maximum supply of oxygen, and the increase in capillary permeability, which usually occurs, drenches the region with blood plasma It would not be profitable to try to present all the reasons for ascribing reactive hyperemia to a number of substances formed continuously in traumatized tissue and usually destroyed *in situ*, so that they do not enter the general circulation in significant amounts unless the local lesion is extensive and serious I believe it is a wholesome point of view—certainly one more in keeping with biological organization in general—to consider that trauma, surely as old an experience for living creatures as the digestion and assimilation of food, immediately induces a local vascular reaction wholly advantageous for restoring the injured tissue to normal This, in one direction at least, is accomplished by the local elaboration of dilator compounds The formation of these compounds is a reasonably continuous process, and the substances formed, though active

in minute amounts, are destroyed so steadily as to preclude their significant entrance into the general circulation, where a wide spread dilatation of capillaries and arterioles would be disastrous for the organism This point of view is my personal opinion relative to a problem far more extensively investigated by others It is based on the idea that injury results in a systematic train of events quite as physiological as that following the now almost forgotten experience of introducing a large piece of rare beef tenderloin into the stomach But perhaps it is presumptuous for a physiologist to declare that inflammation, one of the classical and most cherished possessions of the pathologists, is in reality a normal reaction for which animals are always prepared and from which they derive maximum benefit

There is a further point to be considered in regard to reactive hyperemia, whether brought about by anoxia or by traumatic disruption of tissues This is the fact that the reaction, while occurring rapidly, may be sustained for a long time Glenn, Gilbert and Drinker (3) burned the feet of anesthetized dogs severely by immersion in boiling water, and immediately encased the injured part in liquid plaster of paris, which solidified within five minutes This, of course, resulted in holding the burned foot at normal size It was found that if the cast was removed on the third day, swelling—denoting capillary dilatation—and leakage occurred promptly In such an experiment, six to eight days must pass be fore swelling ceases to follow removal of the plaster This means that in a region violently inflamed by a burn, but treated as effectively as possible and protected against the additive inflam matory effects of infection, the injured tissues continue to give off compounds maintaining reactive hyperemia, and that the capillaries and arterioles most injured by the burn, but still capable of becoming normal, may require a week for recovery This continuance of reactive hyperemia in a well treated lesion of an extremity should be remembered when we contemplate what happens in the lungs when—as a result of anoxia—abnormal vascular leakage begins, and—as a result of the tendency for anoxia to spread— extends through the lung tissues

Return now to facts implicit in the diagram (Figure 9) It is clear that the balance between capillary blood pressure and the osmotic pressure of the blood proteins is such as to make for dryness in the lungs, the dominant tendency being for retention of water by the blood and quick absorption of excessive extravascular water Yet, in the first lecture, I was at pains to describe the extraordinary extent of the pulmonary lymphatic apparatus, an arrangement which ample and satisfactory experiments indicate exists all over the body for the removal of excess blood protein which has leaked into the tissues Can one correlate this profusion of lung lymphatics with the dryness so peculiarly important in the lungs? It is the experience of all who are in good health that the lungs do remain dry, so that the 750 million lung alveoli have a reasonably unobstructed opportunity to receive the inspired air, an equality of opportunity for ventilation which exists only when no factor is present—anoxia, for example—which causes abnormal transudation of fluid from the blood It is equally certain that there is nothing distinctive about the lung capillaries to protect them from the possibility of leaking freely if their supply of oxygen fails The reasons for this leakage are not all inherent in the capillaries but are implicit in their unique setting, the lung tissue

Localized, Persistent Anoxia in the Lungs, Resulting in Capillary Leakage —For their oxygen supply, the body tissues, except the lungs depend upon the arterial blood which, in turn secures oxygen as it passes through the pulmonary capillaries The lungs, a huge collection of ventilating units combined effectively for the aeration of the blood, are in the singular position of depending for the bulk of their oxygen supply upon the oxygen reaching them through the many divisions of the bronchi and the bronchioles It is obvious that exclusion of air from an alveolus occurs most easily if the tube to the alveolus is blocked Very little obstruction may accomplish this Mucus plugs from the secretion of goblet cells may be responsible for obstructing entrance of air More important is the proteinized fluid delivered into the airway through leaky respiratory capillaries

What fundamental conditions are at issue in this

the situation? Turn again to Figure 9 and the 10 mm estimate of capillary pressure As I have said, this estimate is an approximation, since it has not been possible to make measurements of capillary pressure by the direct introduction of a pipette into lung capillary with the chest closed and intrathoracic pressure relations normal The conspicuous net of alveolar capillaries, the *vast surface area they present,* and the absence of any support through tissue pressure make it probable that, even with tremendous changes in the output of the right ventricle, pulmonary capillary pressures increase but little This normal course of events requires adequate and complete alveolar ventilation and no failure of the left ventricle, with a consequent increase in pressure in the pulmonary veins Even though the comparative amounts of air and blood in the lungs may vary reciprocally, rapidly, and to a considerable degree, they apparently return to normal just as rapidly This ready resumption of a seemingly normal state is one of the deceptive elements encountered when appraisal of lung conditions is attempted It is easy to show (4) that on compression of the pulmonary veins there is an instant increase in the flow of lymph from the lungs which means that transudation has occurred When pressure is released, lymph flow falls, but not to normal level for some time, an expression of the fact that something has been left behind which must be disposed of before the lungs are really sound *But by all ordinary means of observation* the animal appears normal, though still under a handicap

There resides in the tissues a factor for the restraint of filtration from the capillaries—a factor hard to measure with any sort of precision, but none the less important for the development of edema This factor is called tissue pressure In the lungs, instead of a positive tissue pressure against outward filtration, the negative *intrathoracic pressure exerts suction upon* the walls of the blood capillaries At the end of expiration, the negative pressure in the chest is −5 mm Hg, and the ensuing normal inspiration reduces this to −10 mm During heavy breathing, −70 mm may easily be reached, and this is usually followed by a forcible expiration, which readily overcomes the negative intrathoracic pressure

normally remaining at full expiration, and may give rise to a positive pressure of 80 or 90 mm Hg These familiar facts in regard to pressures in the chest indicate at once that blood in the lung capillaries is influenced by external conditions in the lungs very different from those existing throughout the areas of distribution of the systemic vessels Obviously, under normal breathing there is a suction element making for filtration in terms of 5 to 10 mm Hg, and this at once wipes out much of the balance for retention and absorption of water inherent in the low capillary pressure, 10 mm. Hg, opposing the 25 to 30 mm. Hg, the normal colloid osmotic pressure It is apparent that the filtering forces playing upon the endothelium of the lung capillaries during quiet breathing are more nearly those of the systemic vessels than has been assumed Graham (5), in 1921, asserted that in patients with some degree of pulmonary edema pleural effusions were readily formed if dyspnea became prominent, the excess fluid in the lungs being sucked through the lung surfaces by the heightened negative pressure accompanying forcible inspiration It, of course, follows that fluid moved into the pleural sacs in this way will be replaced in the lung tissue by a further supply of transudate from the lung capillaries

Notice, however that Graham, in calling attention to the possible effects of the intrathoracic negative pressure in producing pleural effusion, and thereby necessarily increasing pulmonary edema, was discussing a state of affairs in which excessive leakage from the lung capillaries was already occurring His thesis, in reality was that given any increase in capillary permeability, heightened negative pressure inside the chest will prove a formidable contributory factor in the production of pleural effusion and lung edema Confronted with such a rational suggestion, the question at once arises Is this force powerful enough to operate rapidly when there has been no period of chronic, even though slight anoxia ahead of it? I have frequently called attention to the observations of Yamada (6) made upon Japanese soldiers, presumably in good health This investigator reported that he could obtain fluid by thoracentesis in 29 per cent of several hundred men

After severe exercise, pleural fluid was aspirated in 70 per cent of the same group No one has verified these surprising observations and they do not apply certainly to our question, namely, can pressure alone, lacking increased permeability due to anoxia cause pulmonary edema?

During the past two years, Miss Hardenbergh and I have been interested in trying to devise experiments to answer this and allied questions Let me review a little of this difficult cruise, during which it must be acknowledged we have drifted badly more than once Let us, first, follow some experiments in which we attempted to cause pulmonary edema in normal dogs by measures in which filtration pressure and anoxia were contrasted so far as could be managed without radical blockage of bronchi or obstruction of pulmonary veins A dog anesthetized with nembutal was caused to breathe 10 per cent carbon dioxide and 90 per cent oxygen This mixture increased the volume of breathing about fivefold The high percentage of oxygen was employed to preclude the possibility of anoxia in the lungs or elsewhere in the body Resistance to inspiration was then applied by inserting a glass tube containing a small amount of cotton wool in the inspiratory line just outside the inspiratory valve This increased the negative pressure in the chest from 1 6 cm of water to 9 4 cm, and for the next four hours the animal breathed vigorously against resistance to inspiration and with expiration free Blood pressure remained good At the close of the fourth hour the dog was bled to death, and an autopsy done at once The pleural sacs were free of fluid and the lungs showed no signs of edema, merely some degree of congestion in the dependent parts of the lower lobes This means that a normal young dog may be subjected to a long period of forced breathing against resistance, and if the conditions of the experiment prevent anoxia, transudation from lung capillaries though perhaps greater than normal, does not become so large as to result in pleural effusion or pulmonary edema recognizable at autopsy

If the same experiment is carried out in an animal where arrangements have been made to collect lung lymph, an increase

in lymph flow will begin when breathing is stimulated by the carbon dioxide in the respiratory mixture with inspiratory resistance added This is well shown in Figure 10 At autopsy at the close of this experiment, the lungs appeared normal and there was no fluid in the pleural sacs Microscopic sections made from the posterior lowest part of both lower lobes also showed no edema But the increased production of lymph is evidence of augmented filtration from the lung capillaries and since anoxia was prevented by the high concentration of oxygen in the respiratory mixture the increased amount of lymph may be ascribed to the alterations in pressure brought about by the violent breathing against resistance and not to changes in the membrane When the change to artificial respiration was made, the pump used was set so as to match the rate and volume of the breathing under carbon dioxide stimulation with the resistance in place In such an experiment overventilation—achieved by using a positive pressure blast through a tracheal cannula to provide inspiration and permitting expiration to follow passively—may increase lymph formation for a brief time due to the squeezing of formed tissue fluid into lymphatics and out of them but soon the lungs are wrung dry and lymph formation and flow decrease rapidly This experiment in contrast to the first in which lymph was not collected shows that excess tissue fluid can be filtered from lung capillaries in a healthy dog if rather extreme measures are used and if lung lymph is collected to permit functional appraisal of the experiment It is however evident that the ordinary methods for removal of excess tissue fluid by the lymphatics are equal to dealing with the situation since lung edema recognizable by the usual methods of pathology was not present

In a third experiment an anesthetized dog breathed a mixture of 10 per cent oxygen and 90 per cent nitrogen against an inspiratory resistance of 9 cm of water Under these circumstances low blood concentration of oxygen increases breathing somewhat,

[1] For this examination in particular and for constant interest and unfailing patience in keeping a physiologist on a straight track in his excursions through the wilderness of lung pathology I am most grateful to Dr Sidney Farber

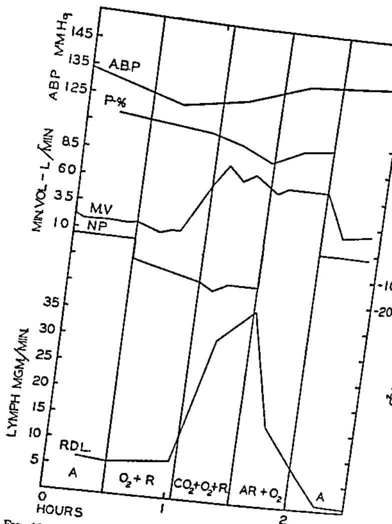


FIG 10—The effects of inspiratory resistance on lymph flow from the lungs *R.D.L.*, right duct lymph in milligrams per minute *A*, air breathed in period from margin of chart to first ... against inspiratory resistance, CO_2+... ture breathed against resistance, *A.R* ... *A*, terminal period breathing air, *N* ... full inspiration in centimeters of wate ... e volume in liters, *P %*, percentage of protein in right duct lymph, *A.B.P.*, arterial blood pressure in millimeters of mercury

making it possible to impose a very considerable degree of inspiratory block and so induce conditions favoring transudation from lung capillaries If the lung lymph flow is measured, it is found to be at once increased, and the high flow is sustained In such an experiment, blood pressure and minute volume of breathing must be measured frequently to be sure that the condition of the animal remains good In our experiments this was done, and there was no deterioration during two and a half hours Oxygen content of the arterial blood averaged 11.3 cc per 100 cc After two and a half hours the dog was bled to death from the femoral artery At autopsy a few cubic centimeters of clear fluid were found in the right pleural sac This had a protein content of 5 4 per cent, and contained enough red cells to induce turbidity but no distinct color The lower lobes of both lungs were heavily congested where they had been in contact with the chest wall along the spine This congestion lessened and disappeared towards the sternal margins of the lobes which had been unimpeded in movement by the supine position of the animal The upper parts of the lungs were normal in appearance except for some degree of dusky congestion over the surfaces against the rigid parts of the chest adjacent to the spine Though the animal was thoroughly exsanguinated at the close of the experiment the cut surfaces of the lungs were very bloody in the dependent congested parts On microscopic examination many of the alveoli and bronchioles in the congested regions contained pink stained slightly granular material in which a very few red and white cells were embedded, and some of the lymphatics were filled with the same substance Here and there alveoli were apparently entirely collapsed Capillaries and larger vessels were overfilled with red cells Anoxia and heightened intrathoracic pressure had undoubtedly produced the beginnings of a fairly widespread region of pulmonary edema with which lymph drainage was beginning to fail to keep pace

In summary, these three experiments are interpreted by us as showing that a normal animal not subjected to circulatory strain—such as would be imposed by exercise or cardiac incompetency—but subjected to a degree of anoxia and resistance to inspiration

not real enough to weaken the circulation, is able to avoid serious pulmonary edema for a long time But the animal does acquire fairly extensive alterations in the lungs from which he would have to recover if permitted to survive the acute experiment Such residua of lung damage—not great enough to affect resting respiratory needs on account of the oversize of the lungs for breathing—though initially not of commanding functional consequence, are potential foci of infection and illness

Let us next examine what may be expected if edema begins to develop in a lung lobule Figure 11 is a photomicrograph of a lung section from a patient dead of pneumonia, a photomicrograph employed by Miller (7) to show that the alveolar epithelium is a continuous sheet of cells, and that openings between the cells—which subsequent to Miller's work have been demonstrated beyond any possibility of doubt—do not exist Certainly the alveolus in the center of the illustration does have an unbroken epithelial border, but the observation is true for this microscopic section alone We need not return to the matter of alveolar pores, discussed fully in the first lecture, but may utilize Miller's section as a very beautiful expression of what happens when transudates or exudates begin to form in the lungs When the lungs contain excess fluid this fluid accumulates necessarily first in the tissue immediately about the lung capillaries This means inside the alveolar walls and throughout the entire respiratory unit of the lungs, including the alveolar ducts, where transuded fluid at once appears in tissue containing lymph capillaries, into which vessels fluid will immediately enter In Figure 11, the epithelium of the central alveolus is shown lifted off as a continuous sheet, and behind it there is a clear space, unquestionably filled with a relatively cell-free exudate during life, but now, due to the shrinking dehydrating processes through which such classical histological specimens pass, existing merely as a narrow space between the alveolar air and the blood in the alveolar capillaries At about seven and eleven o'clock in the central alveolus, it is easy to see how the exudate has thickened the barrier through which gas exchange between alveolar air and compressed alveolar capillaries must be ac

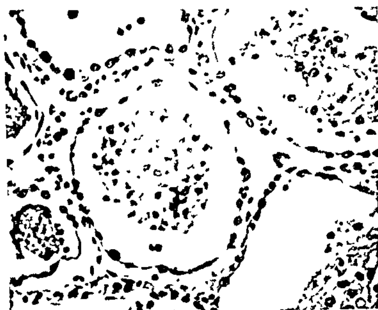


Fig 11—Histological section of a lung from a case of pneumonia The epithelium lining the alveolus in the center of the figure has been pushed off as a continuous sheet Between this membrane and the alveolar wall there is a clear space which in life was filled with fluid from the alveolar capillaries This space thus represents an added barrier to gas exchange between the alveolar air and the blood × 312 (From Miller by permission of the *Journal of Experimental Medicine*, 1925 vol 42 plate 41 fig 1 See also Miller ( ) fig 4" p 63)



FIG 12—Photomicrograph of a lung section from a dog showing extensive lung edema following administration of a thiourea derivative Note the widely dilated lymph channels surrounding blood vessels and bronchioles. X 23

complished In each of the alveoli in the illustration, there is a mass of pneumonic exudate

This section, which has been a source of delight to me as an amateur pathologist looking for structural endorsement of human experience, indicates that just as soon as alveolar capillaries begin to leak the barrier between their walls and the alveolar air becomes thicker True, the added thickness is due to what we call 'tissue fluid,' but it is none the less a wholly abnormal increment to the partition between air and blood in the lungs In these war days, I cannot help recalling a visit to us in the Harvard Laboratory of Physiology made by J S Haldane not long after the first use of poison gas in modern war—the chlorine gas attack by the Germans at Ypres in April, 1915 Haldane had been sent across the channel to see what had happened, to view the casualties, and help decide what must be done to counter one of the most effective surprise offensives ever made He recognized the effects of chlorine immediately, and realized, as did others, that the only way to get oxygen to the men seriously affected was to have them breathe high concentrations of oxygen so as to secure every possible advantage in attempting to aerate the blood through alveolar walls thickened by bloody exudate Haldane's appraisal of the problem seems simple enough to us today in so far as dealing with an acute emergency is concerned But I believe we still fail to realize many of the progressive and insidious subtleties inherent in an advancing state of excess fluid production in the lungs

Fluid in the alveolar partitions is separated from the air by a layer of platelike cells so thin as to have caused prolonged argument as to their continuity in forming an actual wall, and quite incapable of holding back excess fluid One cannot, therefore, be surprised that the air spaces in Figure 11 contain exudate, nor is it unreasonable to expect that in a simple transudation in the lungs, such as attends cardiac failure, the edema fluid passes into the alveoli concurrently with its drift into and along the alveolar walls Everywhere in the body anoxia of capillary endothelium induces increased permeability to water In the lungs, one can readily see how increased permeability may provide a situation

which pushes the process further Fluid in the alveolar walls interferes with aeration of the blood Fluid in the alveoli is even more effective And proteinized fluid reaching bronchioles is worst of all But anoxia is a prime cause for leaky capillaries, and in the lungs there exists a very effective structural and functional arrangement for the propagation of oxygen lack The body is organized to avoid anoxia, and, for good reason, because wherever it occurs anoxia begets anoxia I am sure you can see how pertinent to the problem of pulmonary edema is the spread of anoxia, particularly if you think of the lung lobule as an isolated unit and disregard the collateral connections I have described—connections ordinarily blocked before the clinician enters the problem And obviously no matter how efficacious collateral connections between alveoli may be, *their usefulness for protecting the patient must* disappear when the alveoli are filled with transudate or exudate I view collateral respiration as an invaluable aid in preventing anoxia, but actually, when this protective mechanism is of consequence, it is safe to say that even the most alert clinician fails to realize it When some degree of lung consolidation occurs or when we have little more than cough and trifling uneasiness on the part of the patient it is all too probable that lung lobules somewhere have been cut off from air, and to such a degree that collateral connections have no further effect upon the situation

Ordinarily, most small blockages of respiratory tissue are of little moment They may, however, for two reasons be of great significance to us The first of these reasons rests upon the tendency of the blockages to spread by the drift of transudates or exudates up the airway, with consequent augmentation of anoxia and encouragement of capillary leakage in sound parts of the lungs The second reason for the importance of small blockages of respiratory tissue derives from the fact that different positions of the body affect successful aeration of different parts of the lungs This is true at all times, but particularly when artificial respiration is employed A method while apparently effective at the moment, may leave behind an unappreciated legacy of lung damage

Let us return again to the experimental investigation of transu

dation in the lungs It has always been difficult to make physiological observations on pulmonary edema in animals because it is so hard to devise other than recklessly acute experiments Space does not permit an analysis of the different procedures which produce pulmonary edema in mammalian experiments, but one of them at least merits discussion During the past year, my associates and I have had the good fortune to examine the effects of a substance allied to thiourea This compound is remarkable in that when it is given to dogs by mouth, injected intraperitoneally, subcutaneously, or intravenously, it causes fatal pulmonary edema with pleural effusion—and nothing else When my associates and I were told that a substance existed which could affect the blood capillaries of the lungs and yet not do noticeable harm to the capillaries of the kidney, intestine, liver, or other organs or tissues, it seemed so bizarre a declaration that none of us were impressed But years of experience have taught me never to fail to credit the physiological organization of mammals with the possibility of causing major surprises After satisfying ourselves that this compound, given intravenously, caused pulmonary edema and pleural effusions in dogs, we carried out experiments in which the right lymphatic duct was cannulated so as to collect lung lymph

Figure 13 is the record of a typical experiment, in which blood pressure and minute volume were recorded and lung lymph collected It is difficult to describe the state of mind into which this experiment and others of its sort projected a group of investigators who had been struggling with the task of studying pulmonary edema, but who lacked any reliable means of producing the condition We do not at present propose to present more information on the selective effects of this compound than the facts evident in Figure 13 Two important things may be learned from this experiment first, that lung capillaries possess some quality, either of position or of anatomical constitution, which renders them uniquely vulnerable to the drug or to some compound developed in the body as a result of the injection and second that the lymphatic system in the lungs is ineffectual for draining off a real excess of pulmonary tissue fluid In stressing the first of these

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points, I wish only to emphasize again the need not to be surprised if the blood capillaries in any tissue do not behave, in relation to some fundamental physiological requirement, as they would behave if they were a uniform part of a huge physicochemical system for serving the tissues Possibly the lung capillary endothelium is exactly like that in other parts of the body, if all possible factors could be realized At the moment, how

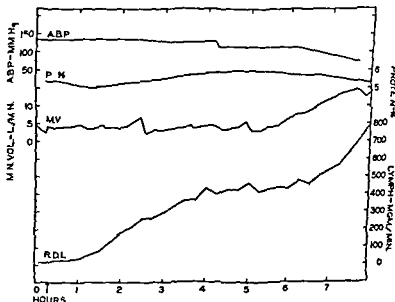


FIG 13 —The effects of a thiourea derivative on lymph flow from the lungs *R.D.L* right duct lymph in milligrams per minute *M V* minute volume in liters per minute *P %* lymph protein in per cent *A.B.P* arterial blood pressure in millimeters of mercury At the upright arrow *260* mg of the finely powdered compound suspended in *26* cc of *6* per cent acacia in physiological salt solution given intravenously

ever, it is necessary to consider that these vessels possess distinctive vulnerability What the total significance of such an idea may be is of course, far beyond our present knowledge, but, in view of the large capacity the lungs possess for engendering disease, any evidence of their specific susceptibility to capillary damage is arresting

The second, and much more definite, fact evident from these last experiments consists in the inadequacy of the lymphatic system in the lungs to keep pace, in terms of removal, with a reasonably steady and rapid production of excess tissue fluid This is not an agreeable picture when one contemplates the situation of a man who has inhaled a dangerous amount of chlorine, nitrogen dioxide, or phosgene—any one of which may be encountered in industrial accidents

In the experiment which is our text, a dog anesthetized with nembutal was prepared for observation by cannulating the trachea for respiratory measurements, a femoral artery for recording blood pressure, and the right lymphatic duct for collection of lung lymph In order to avoid anoxia, the dog was made to breathe 100 per cent oxygen throughout the experiment At the point indicated by the arrow on the base line, 260 mg of finely powdered material suspended in 26 cc of a 6 per cent acacia physiological saline solution were given intravenously The dog weighed 13 kg, and previous experiments had shown that 10 mg of the drug per kilogram, given intravenously, begins to cause pulmonary edema in from one to two hours, but does not lower blood pressure or affect breathing, except to a slight degree immediately after administration The compound is exceedingly insoluble in water It must be ground finely, and while it settles slowly in the acacia solution the particles remain fairly discreet, and if shaken before injecting are well distributed in the liquid Owing probably to the insolubility, a suspension such as the one used intravenously in this experiment may be given intraperitoneally without causing pain and twelve to twenty hours later, when the animal has succumbed to pulmonary edema and pleural effusion, no evidence of other than a slight foreign body reaction is found in the peritoneal cavity and the injected material has almost entirely disappeared

When a suspension of foreign particles of any kind is injected intravenously in a dog, the particles are removed from the circulation within thirty minutes, and can easily be found in the Kupfer cells lining the liver capillaries (8) Since the thiourea derivative is a very insoluble crystalloid, it is easy to see the crystals in liver

sections viewed under polarized light Very few particles are arrested in the lungs In Figure 13, it is evident that once lymph *flow from the lungs of the injected* animal began to increase, the process continued with gathering intensity for hours Notice that minute volume—aside from minor fluctuations due usually to the depth of anesthesia—did not rise substantially for about six hours and that shortly after this arterial blood pressure began to fall Blood gas concentrations were not measured in the experiment, but it was noted that the arterial blood remained bright red *until near the end when the animal was bled to death It is obvious* that the 100 per cent oxygen used for ventilation was of assistance to the animal since the early addition of anoxia would have resulted in disaster much more quickly In this dog, the protein in the lung lymph was very high before the administration of the drug, so also was the protein in the blood, being 7 3 per cent It is noteworthy that protein in the lung lymph did not rise substantially, and that at autopsy the protein concentrations in lung lymph, in fluid from the pleural sacs, and in fluid from the trachea were identical

There was no free fluid in the abdomen, and the abdominal organs were normal Urine was secreted throughout the experiment *The heart was undamaged, and there was no* excess fluid in the pericardial sac One hundred and thirty cc of yellowish pleural fluid were removed from the chest This contained very few red and white cells being apparently a pure transudate During the experiment the lung lymph remained equally low in cells, and the *frothy fluid from the trachea was not blood* tinged In our experience with the effects of this remarkable agent, there is little loss of cells from the blood into the lymph and into the pleural sacs until near the end when anoxia begins to be pronounced At this time bloody froth appears in the trachea and death is not long postponed

The lungs removed at the close of this experiment were an astonishing spectacle The record of lymph flow from the right duct which had steadily increased through seven hours to reach a rate such as one obtains from the thoracic duct in a satisfactory experiment, indicated that *the lung capillaries were highly perme-*

able to plasma, and that the employment of oxygen for ventilation had permitted adverse conditions in the lungs to develop slowly Both lower lobes throughout, and all the lung tissue resting upon the thoracic wall was solidly incollapsible, resembling very stiff jelly The same condition extended toward the free margins of the lungs under the sternum, and at the close of the experiment the *respiratory exchange in this dog depended upon this fraction of* the lung tissue At the roots of the lungs, and wherever bronchi or blood vessels could be seen, they were inside a shrouding capsule of clear yellow fluid When the lungs were sectioned, blood vessels and bronchi protruded from the gelatinous cut surface surrounded by a halo of clear jelly, probably entirely fluid during life In the case of the largest vessels and bronchi, this encircling clear zone was sometimes 5 mm across As the air passages and vessels grew smaller, the surrounding clear zone remained proportionately prominent Figure 12 (facing p 37) is a section from a lower lobe, which grossly was solid and contained no air The feature of this section is obviously the wide space which surrounds bronchioles and vessels It is a greatly dilated lymph channel

All of this gross and microscopic observation led to but one conclusion—that the lymphatic draining trunks had been far overfilled, and had existed as continuous thick sleeves of transudate around the structures with which they were associated It was plain beyond question that the normal pathway of lymph drainage was quite inadequate to deal with the deluge of transudate which had entered it In the first lecture, I called your attention to the fact that lymph flow from both lungs is directed to the right lymphatic duct, a short narrow channel entering the right sub clavian vein just above the apex of the right lung The dilated, overfilled lymphatics in this experiment had to deliver their con tents to the blood through a veritable bottleneck, and this method for clearing the lungs of excess fluid broke down There remained but one other wide path for escape of transudate—one, as has been pointed out, all too easily entered—the airway Flooding of this route leads to but one end, death by asphyxia, the in evitable final event in unchecked pulmonary edema

In summary, it has been my purpose in this lecture to show that

1 Anoxia, a cause of excessive capillary leakage all over the body, is effective in the lungs

2. Increased pressure in the pulmonary capillaries does not readily cause recognizable pulmonary edema unless coupled with heightened permeability, most frequently due to anoxia

3 Localized regions of edema can and do easily occur in the lungs without noticeably affecting breathing

4 In a new compound allied to thiourea we possess a specific for causing pulmonary edema and pleural effusion With this compound administered intravenously, it can be shown that when lung capillary leakage of proteinized fluid is excessive and continuous, the lymphatic drainage route from the lungs becomes inadequate, leaving no line of outflow except through the air passages—a way of fluid removal which means progressive exclusion of air and eventual death

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III

BREATHING MOVEMENTS AND PULMONARY EDEMA

In the last lecture I showed that a means is available, through the flow of lung lymph, for appreciating the earliest phases of excessive leakage from the lung capillaries This makes it appropriate to review some general matters relative to lymph formation and flow

When water leaves the blood in all parts of the body to become tissue fluid, its next movement depends upon very diverse conditions It may become intracellular, it may be reabsorbed into the blood, it may exist as tissue fluid scant in amount and drifting but little through the tissues or it may enter lymph capillaries and eventually be moved along the lymphatics through lymph nodes back to the blood There is no fixed path for extravascular water In a seemingly casual manner, it finds its way to whatever functional requirement calls most avidly for it Only a small fraction of the water which leaves the blood becomes involved in the formation of lymph and in no part of the body can lymph drainage make substantial headway in relieving edema due to abnormal transudation from the blood I showed in the last lecture how disastrously this fact may display itself in the lungs, where edema is not simply an awkward load upon local function but may progressively abolish the possibility of function

Adult mammals do not have lymph hearts The lymphatics at the periphery of the mammalian lymphatic system form nets of continuously walled capillaries, wider in diameter than blood capillaries and with walls which many experiments have shown are permeable to almost anything in the tissue in which they exist In that it is derived from the blood, the formation of lymph is no

different from the formation of tissue fluid There are practically no valves in the nets of lymph capillaries The direction of lymph flow in them is dependent upon gravity, upon tissue pressure, and upon such forces as are applied by massage and movement of the part The capillary nets connect with somewhat narrow and thicker vessels which are valved In regions, such as the legs where there is a relatively steady gravitational pull away from the heart, these vessels are extensively valved so as to assure lymph movement in but one direction—towards the heart At the same time, these draining trunks are weak and tenuous structures, easily stretched so that the valves become incompetent and localized stasis results But the draining vessels are so numerous at such different levels, and so interconnected as to make it impossible to block all of them, save through the persistent attacks of chronic disease or through repeated intralymphatic injections in experiments patterned upon the processes of chronic inflammatory disease Only in the lungs do we find the final outlet for lymph—the right lymphatic duct, exceedingly small and very close to a huge system of draining trunks

In most parts of the body the flow of lymph in the valved conducting vessels is dependent upon forces outside the lymphatic system Motion and massage operate in the lungs just as they do elsewhere in the body The formation of lymph in the lungs thus depends upon the permeability of the endothelium of the capillaries and upon intracapillary pressure, increased by the suction exerted through the negative intrathoracic pressure The flow of lymph toward its point of drainage into the blood depends upon the movements of the lungs during breathing possibly to a slight degree upon pulsation of the pulmonary arteries and, when lung edema has developed, upon positive tissue pressure

I have attempted to show that appreciable lung edema, detected through our usual means of observation, spells the fact that lymphatic removal of transudate has failed to carry off the excess fluid in the lungs Since movement of lymph through lung lymphatics is dependent upon respiratory movements, it is now essential to analyze the effects of different sorts of breathing on the forma

tion and flow of lymph In our consideration of pressure effects for filtration from the lung capillaries, I showed a diagram of an experiment, Figure 10, in which a dog was subjected to increased resistance to inspiration while expiration remained normal A breathing load of the sort described imposed upon a mammal slows and lengthens inspiration and the expiration which follows although unimpeded is often forcible The facts are that if inspiration is blocked there will be a generalized increase in the flow of fluid from the pulmonary capillaries into the lung tissues and back to the blood via the lymphatics This increase depends upon increased formation of tissue fluid during inspiration and squeezing of lymph toward the right duct if vigorous expiration follows These effects are of course, related directly to the extent of inspiratory block imposed

While breathing naturally a normal dog under complete anesthesia produces but a few milligrams of lymph per minute from the lungs The flow is frequently so slight as to cause the investigator to wonder whether his cannula is really in the right lymphatic duct In such a predicament, if arrangements have been made to substitute artificial respiration for natural breathing, lymph flow will increase mightily on the first positive strokes of the respiratory pump and the investigator can thus assure himself that his cannula is in the line of lung lymph drainage

Why does lymph flow from the lungs increase when artificial respiration is instituted by the usual positive pressure blast delivered through a tracheal cannula? It is easy to see that positive pressure breathing squeezes the lung tissue against the thoracic walls has, in fact a massage effect upon the draining lymphatic trunks not at all unlike that imposed upon a leg by vigorous massage In many experiments Miss Hardenbergh and I have cannulated the right lymphatic duct and have measured the rate and volume of natural breathing in the anesthetized dog Then, by means of a specially constructed respiration pump it has been possible to shift to positive pressure artificial respiration at the same rate and volume of the animal s natural respiration Expiration with this pump is without suction just as in the dog under

natural breathing It is an observation for later comment that when one makes such an adroit shift, the ventilation supplied by positive pressure artificial breathing is always inadequate, and the animal continues to make efforts to breathe until the minute volume supplied is increased

Many such experiments show what the slightest consideration of the problem suggests Whether artificial respiration through positive pressure accomplishes adequate, inadequate, or excessive lung ventilation, the massaging effects of the positive pressure blast compress the lungs against the chest and drive lymph along valved draining trunks When positive pressure breathing replaces natural or negative pressure breathing, one may expect an immediate increase in flow of lung lymph, which in turn reflects a general wringing out of the lungs, with consequent movement of tissue fluid and lymph It is of interest, and the issue should be followed further, that in lungs where increased tissue fluid production from the capillaries is not occurring, positive pressure respiration without suction in expiration increases lymph flow briefly, and results eventually in extinction of flow This depends upon the fact that the positive pressure ventilation has reduced transudation from the lung capillaries If, however, positive pressure artificial respiration is applied when lung capillaries are leaking abnormally, then the effect of the artificial respiration will be a steady increase in lymph flow, accomplished by pressing fluid through the lungs for outflow from the lymphatics Further, if positive pressure is followed by suction, lymph production and lymph flow continue steadily and in amounts above normal

From such positive effects of breathing, we may turn now to the question of lymph flow from the lungs when breathing movements are absent In dogs with the chest open and under artificial respiration, Warren and Drinker (1) showed that if the rhythmic movements of the lungs were stopped by substituting continuous insufflation of oxygen, thus holding the lungs about two thirds inflated and motionless, lymph flow soon ceased This observation is important in relation to pneumothorax, whether accidental or therapeutic Wherever lung movement ceases lymph drainage

from the region stops, unless, as will be the case in inflammation due to a thriving infection, exudation develops localized tissue pressure, which again induces lymph movement

In Figure 14, an experiment is illustrated in which breathing movements were first altered by imposing resistance to expiration, and then by adding resistance to inspiration These resistances were applied beyond the respiratory valves connected with the tracheal cannula The second situation, in effect, was equivalent to a partial obstruction of the trachea In this experiment the right lymphatic duct was cannulated to collect lung lymph, and the dog, under nembutal anesthesia, breathed 100 per cent oxygen through a tracheal cannula Arrangements permitted measurement of the volume of breathing and blood pressure Resistance to breathing, both inspiratory and expiratory, was measured by means of a water manometer connected with the trachea We have thought it unwise in experiments such as this, to puncture the chest wall in order to measure intrathoracic pressure directly, and have utilized instead to indicate conditions in the chest intrapulmonic pressure measurements

Lymph flow in the experiment pictured in Figure 14 was characteristically low during thirty minutes of normal breathing Resistance to expiration was then imposed This procedure decreased minute volume of breathing somewhat, but did not disturb the circulation As a result of the forcible expiratory efforts, lymph flow increased at first, and then began to fall until inspiration also was partially blocked, when lymph flow again increased

It is not hard to explain what is shown by this experiment When expiration is opposed, the dog immediately begins to use his respiratory muscles to force air out He makes a muscular effort, instead of the passive elastic recoil which ordinarily contrives expiration This positive squeezing out of air results in driving lymph along drainage channels Lymph flow increases promptly and then begins to fall This means that the massaging effects of forcible expiration force lymph toward the right duct where it is collected At the same time, inspiration increases somewhat in order to meet the respiratory needs of the animal, and

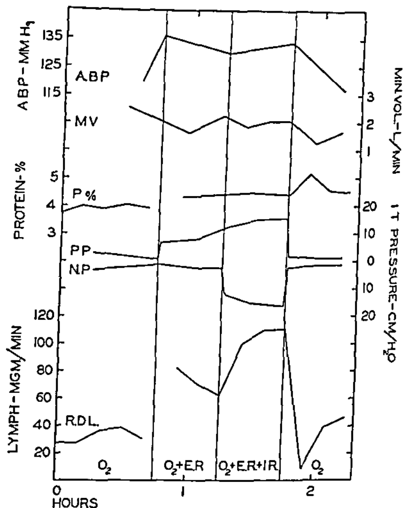


FIG 14—The effects of expiratory and inspiratory resistance on lymph

breathed without resistance, *N.P*, intratracheal pressure in centimeters of water, negative, *P.P*, intratracheal pressure in centimeters of water positive, *P*-%, per cent of protein in right duct lymph, *M V*, minute volume in liters per minute, *A.B.P*, arterial blood pressure in milligrams of mercury

production of lymph, dependent upon transudation from the lung capillaries, though diminishing, continues So it results, if breathing against expiratory resistance is continued, that lymph drainage from the lungs first rises as lymph in the lymphatics is milked out This increased delivery of lymph would disappear were it not for the fact that in the naturally breathing animal it is not possible to alter one phase of respiration without to some degree affecting the other When inspiratory resistance is added to expiratory, lymph flow rises again, and under these circumstances the heightened movement of lymph will continue since increased negative pressure in the chest provides a supply of tissue fluid to become lymph

These demonstrations of the movements of lymph and the formation of lymph under different conditions of breathing carry lessons which apply practically to the management of many situations met in disease and to the use of protective equipment both in industrial processes and in war When motion of a lung or part of a lung ceases, spread of tissue fluid and formation and movement of lymph are all much restricted It is essentially a physiological arrangement for localization of trouble, just as is complete immobilization in any part of the body

Under the conditions of disease, it is rare for developments to arise which obstruct inspiration or expiration alone, as is easily done experimentally Usually the air passages—and this means from the largest down to the smallest—become occluded by inhaled material, by exudate, or by transudate Such a situation, whether involving but a small section of lung or an entire lobe, results, as long as the circulation of the unaerated tissue continues, in increased production of tissue fluid—fluid which diffuses through the affected lung into draining lymphatics and away from the original focus of anoxic damage

Leading, as they do, to capillary leakage with respiratory changes which not only enhance the production of tissue fluid but also increase delivery of this fluid along the lymphatics, the events which follow blockage of air passages combine all the effects of anoxia Visualize, for example, the train of events which

is immediately set in operation when a man inhales a lung irritant such as chlorine, the fate of the Canadian soldiers in the trenches at Ypres in 1915 The gas affects the mucosa from the top of the respiratory tract to the alveoli This means increased formation of mucus, turgescence of the mucosa, perhaps direct stimulation of the smooth muscle of the bronchioles with resulting contraction All this results in blockage of air passages and anoxia of alveolar capillaries, but, here again, the one most prominent effect is increased delivery of proteinized fluid, which adds to the exclusion of air and the cycle of disaster

There is another issue in relation to breathing and the development of abnormal conditions in the lungs more subtle than the rather definite influences upon extravascular fluid movement which I have described

Position as a Cause of Blood Stasis, Atelectasis and Pulmonary Edema —Man does most of his breathing in the erect position He achieves the easiest and most complete ventilation of his lungs when he stands or sits His vital capacity is greatest in the erect position When he experiences distress in getting sufficient air, he invariably sits up

Not only does man prefer the erect position for ease in breathing so that he may most easily ventilate all his lung tissue, but, if he has remained quiet for a long time, without the possibility of movement, he indulges often in a long breath, a sigh, or a yawn Some years ago I watched a highly intelligent young man undergo the 'first prolonged experience in the respirator devised by my brother At that time no one had any way of predicting how a helpless young man, lying on his back on a thin mattress inside a small metal cylinder, would get along or what he would need from the man controlled device which had been substituted for his respiratory center and beautifully coordinated muscles of respiration When this first patient was placed in the first respirator, inspiration was induced by suction with a pump, followed by positive pressure to force air out From the beginning the patient disliked the pressure expiration, this was, therefore, cut out and expiration allowed to be passive as in natural quiet breathing A more interest

ing matter relating to the comfort of the young man, who spent a long time in the respirator before recovering, was his request that from time to time the respirator be made to give him a deep inspiration, a sort of prolonged yawn or sigh This gave comfort to him, and thought to me

Here was a young man, supine and incapable of motion, who was made more comfortable if from time to time his lung ventilation was radically altered during a few breaths In sleep all of us move about, snore for a while on our backs, then turn to one side, stop snoring or, at least, begin a new symphonic movement, then turn again, and so on through the night When you think about it, you realize that man is never absolutely sure to remain still physically for any length of time unless he is anesthetized or dead In the first of these human experiences, we are responsible not only for the initiation but also for the duration of the period of inert, unchanged quiescence to which surgical patients must submit Sleep differs from anesthesia in that the sleeper still is his natural self He turns and twists and snores and groans because he needs to do these things But the patient under an anesthetic, the drunken man in his oblivion, the patient dangerously asphyxiated by carbon monoxide, all these have lost a part in the regulation of breathing When a physician gives an anesthetic, he has more than the apparently simple obligation of getting a patient through an operation, he must also think of every factor which will result in complete ventilation of all parts of the lungs He must be like the man who found his lost mule just by going to where he would have gone had he been a mule! A good anesthetist is a person who by knowledge or instinct is really breathing for his patient He has had the temerity to become the oxygen supplier of another individual, and nature provides many traps for him

Medicine has advanced mightily since I graduated in 1913 Insulin, liver extract, sulfa compounds, penicillin, what a group of constellations to light our hopes! But do not let these brilliancies cloud your perceptions of small, pressing, every day matters

On August 19, the Journal of the American Medical Association

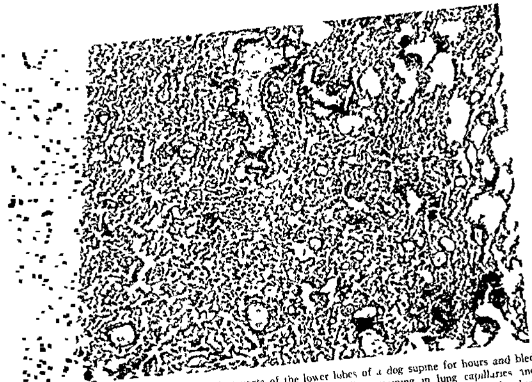


Fig. 15.—Photomicrograph of dependent parts of the lower lobes of a dog supine for hours and bled to death while in good condition. Note the abundance of red cells remaining in lung capillaries and larger vessels indicating that circulation through this part of the lung was at best extremely sluggish at the time of final exsanguination. × 100



Fig 16—Same

patient with decompensating mitral stenosis with the right ventricle still fairly capable In such a patient, abnormal pressure increase in the capillaries, aided by anoxia, results in edema, which progresses as blood is forced into the leaky vessels

No such sequence of events is involved in the overquiet anesthetized dog the subject of our experiment In the small vessels at the bases of his lungs, there is the typical picture of stasis which Krogh described as a physiological entity in 1922 (4) If one causes stasis in the web of a frog while observing the capillaries under the microscope, it is soon apparent that recovery from the condition depends upon the degree of damage suffered by the endothelium If this is slight and the full force of arterial blood flow allowed to reach the region of stasis, one may watch the packed red cells forced along vessels in the most casual manner, evidently conversion of noncirculated to circulated capillaries But where red cells have become tightly packed, many of the vessels remain permanently blocked

One cannot predict how readily such a focus of altered, though perhaps not seriously damaged lung as that of our dog will become normal Suppose, for example, that instead of a healthy young dog as subject, we consider what might happen in the case of an elderly patient compelled to undergo a laparotomy lasting an hour or more The chest of such a patient may be assumed to be somewhat rigid and immobile as compared with that of a young adult Pain from the laparotomy adds to the restriction of breathing As Dock (3) has pointed out, the changes we have observed so constantly in anesthetized animals of all sorts, occur equally readily in man, perhaps more readily in the more vulnerable elderly subjects And these last patients, by their very age and inelasticity, will have the poorest capacity to get rid of the pulmonary handicap the anesthesia and operation have left with them It is no wonder that such persons drift stealthily into diffuse inflammatory conditions of the lungs Anoxia begets anoxia, and when the setting has been provided so that infectious inflammation sets in, then a growing compelling process begins to threaten And how, in the end, does the extending process act if viewed physiologically? It

acts by the simple and fatal propagation of anoxia in the lungs until eventually so much aerating surface is excluded from the air that the oxygen of the arterial blood begins to fall and death is at hand

Let me speak now of conditions in connection with breathing which will promote the train of events we have been discussing Our problem concerns the breathing and the state of the lungs in a patient under surgical anesthesia or unconscious and immobile from accident or disease

Shallow Breathing—One of the many causes of disaster to the breathing mechanism of men, appreciated fully by J S Haldane (5) and discussed in his classical monograph on respiration, is shallow breathing Haldane first established the fact that as a man experiences generalized anoxemia, his "respiratory centre becomes very easily susceptible to fatigue, as manifested by diminishing depth of the breathing" But shallow breathing—this expression of the effect of anoxemia upon the respiratory center—by its very existence enhances anoxemia In the lungs of a patient lying motionless on his back, shallow breathing means extinction of air entrance into many lung lobules, and any protective effect which might arise from collateral respiration suffers coincidentally

Blockage of the Air Passages—In a patient experiencing localized blockage of bronchi or bronchioles, when, at the same time ventilation of the lobules involved is restricted by position, the part of the lung involved is unquestionably in sore straits We have shown how increased inspiratory negative pressure, such as comes from inspiring against resistance, increases leakage from lung capillaries, and how forcible expiration, such as occurs against resistance, promotes lymph flow This arrangement for drainage is toward removal of edema, but, as we have also tried to show, may not keep pace with local developments The result of these facts amounts to the inevitable conclusion that a man with any condition leading to localized obstruction of air passages, and subjected to anesthesia or to any experience in which position is unchanged and breathing at a steady minimum, is under increasing threat

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from mounting capillary stasis and atelectasis with advancing pulmonary edema

Artificial Respiration by Means of Apparatus Designed to Accomplish Inspiration by Blowing Oxygen Air Mixture into the Lungs, Followed by Suction to Accomplish Expiration—The group of patients desperately in need of improvement of breathing and treated by the resurrected pulmotors—now called resuscitators—is fortunately small The great majority of victims encountering such devices are either so little in need of assistance as to be virtually unaffected by the appliance, or else they are dead The result of these circumstances has been to give the impression that of patients treated by resuscitators a large number—the group who in reality needed no assistance—have been saved A second group upon whom treatment was attempted were safely in their last rest before being subjected to this modern agency for resurrection so that nothing could have helped them Admitting that no mechanical appliance, even with the endorsement of the American Medical Association, can raise the dead, the record of apparently successful treatments is favorable to the appliance I do not wish to argue about the usefulness of a device which has had such authoritative endorsement (6) as these blow and suck resuscitators[1] I do, however want to point out that no combination of breathing measures we have been able to apply in the form of artificial respiration is so effective for inducing pulmonary transudation and spread of tissue fluid as mild positive blast inspiration under automatic safety control so that the blast cannot become forcible enough to reach the alveoli if slight obstruction is present, followed by suction to produce expiration In discussing artificial respiration I will bring out the ventilatory defects of blow and suck devices At this time I wish merely to indicate their potentiality for spreading infectious processes through the lungs If used upon inert supine patients resuscitators are perfectly

[1] The statements which follow must be understood to be based upon experiments and observations by the author They are in disagreement with assertions of the Council on Physical Therapy of the American Medical Association and their consequent validity is thus of necessity left to the judgment of the reader

organized to add to already present lung lesions, from which the patient must recover if he survives acute asphyxia

Contrasting with the factors which have been described as adding to blood stasis and atelectasis in the posterior and lower parts of the lungs of supine, immobile, and unconscious patients—conscious patients may also be affected—there are obvious factors which prevent such developments

Change of Position —Change of position has long been recognized as imperatively necessary in postoperative care, particularly of old people The degree to which position can be changed depends upon circumstances and, above all, upon intelligent nursing It is easy to show by animal experiments that if an anesthetized dog is laid belly down upon the operating table, instead of on his back stasis and atelectasis are shifted to the sternal margins of the lungs If, too, a dog lying supine during an operation is bandaged from the lower part of the abdomen toward the head so as to restrict breathing movements even more than is accomplished by position alone, then the lesions we are following will become much more extensive, reaching widely through the tissue immobilized by the binder

A very simple experiment is instructive A dog anesthetized with nembutal was bandaged to restrict his breathing somewhat, and was placed on his back on the operating table as shown in Figure 17 This experimental setup interfered with breathing, not only through the supine position, but because the binder still further immobilized the lower parts of the lungs The total handicap to breathing was of no general consequence to the healthy young animal used in the experiment, but did cause lung changes, evident in Figures 18 19, and 20 Figure 18 is a photograph of the lungs removed from this dog at the close of the experiment It shows the lungs in a normal degree of inflation—accomplished by very careful removal of these organs from the chest with the trachea clamped, plus slight additional inflation The lower and posterior parts of the lungs were deep red, the most dependent part of the left lung just visible in the photograph, being solidly red and apparently unventilated



Fig. 17.—A dog under surgical anesthesia from nembutal breathing air and with an abdominal bandage extending over the lower margins of the ribs was allowed to remain in the position shown for five hours One minute following injection of 22 cc of an acacia graphite suspension into an external jugular vein the dog was sacrificed by bleeding from the femoral artery every care being taken to make exsanguination as complete as possible

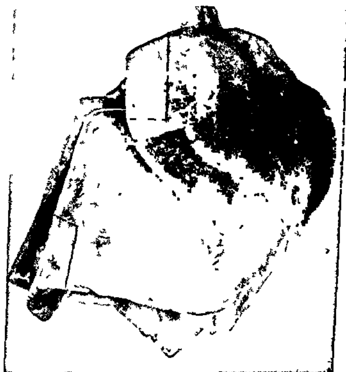


Fig 18 —The gross appearance of the lungs of the dog shown in Figure 17 To preserve normal appearance the trachea was clamped before opening the chest and in order to ascertain the possibility of air entrance into abnormal lung tissue the lungs were slightly inflated after removal The squares mapped *in the illustration were laid out by paper markers photographed* on the lungs prior to sectioning and show the regions from which blocks of tissue were taken for microscopic examination Right lung lateral view

But let us return to the experiment At the end of five hours, 22 cc of a suspension of very finely divided graphite in 6 per cent acacia physiological saline was injected rapidly into an external jugular vein Since graphite particles, in contrast to the usual carbon of our black drawing inks, agglutinate very little in the blood, such an injection does not disturb the dog It enters the right ventricle and is at once driven through the lungs, following the vascular paths in use by the animal at the time of the injection One minute after completing the injection of graphite in the experiment under description, the dog was rapidly bled to death by opening a femoral artery At autopsy the lungs showed the usual dark red discoloration along the posterior part, the most dependent during the long anesthesia Owing to the binder, the congestion extended laterally more than would usually be the case In Figure 18, one margin of this condition in the right lung is easily seen In the fresh specimen the large amount of graphite in the normal upper part of the lungs, where the circulation and ventilation were normal, was striking as compared with the practical absence of black coloration in the congested tissue Figure 19 is a photomicrograph of a section from the upper lobe as outlined in Figure 18 Figure 20 shows the condition of the lung in the congested tissue at the base This latter section was cut from the block outlined in Figure 18 at the right base It is obvious that the graphite, a physiological injection mass, flowed freely through the capillaries in the sound part of the lung but entered the livid lower part of the lung to a very limited degree

In 1929, Coryllos and Birnbaum (7) apparently realized the passive nature of the changes in the compressed parts of the lungs due to position, but their long involved paper is chiefly valuable for its extensive bibliography

Deep Breathing —Dock (3) has pointed out that when patients have been breathing deeply, they are less liable to have pulmonary complications than if their breathing has been feeble Respiratory movements of different depth and character coming from time to time in a conscious patient—a yawn, a sigh, or a cough—may change the degree of alveolar ventilation in a part of the lung

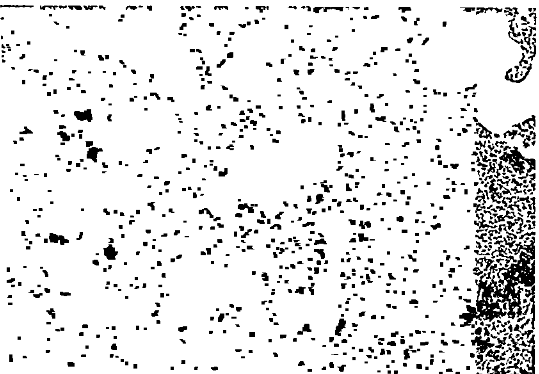


Fig. 20.—Photomicrograph of section from posterior and lowest part of right lower lobe, as outlined in Figure 18. There is atelectasis and stasis, and the relatively few graphite particles are concentrated in large vessels and not diffusely scattered through the tissue. This indicates the scanty blood flow through the region at the time of the injection. × 152

4 KROGH, A. The Anatomy and Physiology of Capillaries Yale University Press, New Haven, 1922, Revised and Enlarged Ed, 1929
5 HALDANE, J S, and PRIESTLEY, J G Respiration New Ed Yale University Press, New Haven, 1935, p 205
6 COUNCIL ON PHYSICAL THERAPY, AMERICAN MEDICAL ASSOCIATION E & J resuscitator, inhalator, aspirator (Fox model) acceptable *J Am Med Assn*, 1943, **121**, 1219
7 CORYLLOS, P N, and BIRNBAUM G L The circulation in the compressed, atelectatic and pneumonic lung (pneumothorax-apneumatosis pneumonia) *Arch Surg*, 1929, **19**, 1346

IV

PREVENTIVE AND THERAPEUTIC MEASURES IN ASPHYXIATING PULMONARY DISEASE

THESE LECTURES, to this point, have described local conditions in the lungs, together with distinctive anatomical and physiological peculiarities which make for initiation and propagation of different lung conditions. Experiments have been described which show the relation between different common variations in breathing and their effects in causing filtration of fluid from the alveolar capillaries. In all of this discussion, while pressure variations in the capillaries and the ways they occur have been prominent, it has, I hope, been made clear that, since anoxemia increases capillary permeability and leads to increased leakage even under conditions of normal pressure, the local experience of anoxia is a potent threat to the maintenance of normal respiratory exchange in the lung lobules. But obviously, if lung structure and breathing movements influence pulmonary conditions and lead frequently to anoxia, in a discussion of the therapy of asphyxiating pulmonary disease, one must consider not only these issues but the regulation of breathing as well.

Space and time do not permit an extensive review of the physiology of respiration, nor would most of such a review be pertinent to problems of fluid production and removal in the lungs. And so, I shall select those features of the physiology of breathing, which, from my experience in the clinic and laboratory, appear important to me. It goes without saying that my opinions are worth no more than your appraisal of their rationality. One of the most attractive features of medicine for many of you who cerebrate upon a liberal pattern is the fact that no one confronted by a medical problem is ever wholly right. Carried further, this is the reason why the best scientists are *the truest liberals*. They

strive to the end of their days to learn an answer, but even if they weigh their ultimate accomplishment to many decimal places, there is always a haunting question mark at the end of the calculation No liberal thinker has an assured end for his thoughts or actions This does not mean lack of motivating conviction in work The investigator will lose nothing by believing he is on the right path, but he ceases to be a liberal thinker as soon as he is dismayed or surprised if what he discovers goes against his beliefs Liberalism, in the truest sense, is the expression of a receptive mentality—a mentality ready to meet new problems by fair, fresh appraisal, willing to make decisions, using all the knowledge from the past that can be applied to the research of the moment, but undismayed by the result

I have indulged in this digression because of my hope that these lectures will cause you to think, and so to be dissatisfied with what you have been taught and what you know There is an impression that a Harvard professor is characterized by three attributes, not ones of chance but of fact He wears a red necktie, his trousers do not fit, and he is invariably right! To the first two of these qualifications I often conform—or so goes the report—but for the third, I am a veritable Mr Milquetoast, labelled from Harvard, but innocent of assured knowledge

Having thus sowed a wholesome skepticism relative to what I shall say, it follows that I shall say exactly what seems most suggestive and useful to me

The breathing of mammals depends upon the localization in the medulla of an automatic collection of nerve cells called the respiratory center The term automatic is used because, from this small group of nerve cells, fibers, and synapses, rhythmic impulses are sent out which result in inspiration This actively engendered inspiration is followed by passive expiration The apparent independent automaticity of the respiratory center is known to be the expression of a multitude of factors in the center itself and of factors playing upon the center So far as I can see, the respiratory center is an actively metabolizing unit of nerve cells, synapses, and nerve fibers It has been found that the oxygen requirements

of such nerve tissues are high We may therefore set out with the principle before us that the respiratory center itself, the director of body oxygenation, must be well supplied with oxygen if it is to perform acceptably

In a previous lecture I called attention to the fact that J S Haldane (1) recognized the vulnerability of the respiratory center to oxygen lack The cells of the center must dip from a bountiful supply of oxygen in the arterial blood in order to give their messages for the breathing movements which will result in the blood aeration they themselves require If oxygen begins to fall in the arterial blood, the chemoreceptors in the aortic and carotid bodies become active, and somehow or other cause the respiratory center itself to become more active, even though under the handicap of anoxia The reenforcement of the center from these outlying sources is rugged and persistent But they are props, not joists, in the respiratory skyscraper The fact is that if an animal or man is caused to breathe air deficient in oxygen so that the result is protracted oxygen lack, the potentiality of trouble develops The first evidence of this is an increase in the minute volume of breathing Respiration next becomes irregular, and eventually rapid and shallow These changes express the fact that the normal process of nerve impulse discharge from the respiratory center due to carbon dioxide accumulation becomes disorganized when the tissue does not receive enough oxygen The histological structure of the respiratory center is an infinitely complex melange of cells, synapses and fibers That free intercommunication of neurological units is essential for functional success is old knowledge, and that fatigue—or, better, difficulty in transmission from one neurological unit to another—is most readily due to synaptic block is a fact whose recognition goes back to Sherrington (2)

The respiratory center is stimulated by carbon dioxide and hydrogen ions When anoxemia causes increased breathing it does so through nerve impulses arising in the chemoreceptors of the carotid and aortic bodies The way in which nerve impulses stimulate breathing, whether by accomplishing a reflex contact with efferent neurones in the center, or by nerve impulses which in some

way or other sensitize the center or depress it, so that the normal stimulus for breathing is created more readily or—if the particular nerves are inhibitory—less readily, is not certainly known Whatever the ultimate physiological explanation may be, there is no doubt the center fluctuates in irritability We describe this by saying that the threshold of the center for stimulation varies For example, if a dog breathes carbon monoxide until his blood has lost 50 per cent of capacity to carry oxygen, his respiratory center, along with the rest of his body, the lungs excepted, suffers from oxygen lack His blood pressure may be little affected and the output of the heart still good But if, under this serious degree of anoxia, 10 per cent carbon dioxide in air is breathed, though respiratory volume is increased, the effectiveness of the normal stimulant to the center—carbon dioxide—is far less than was the case at the outset of the experiment and prior to the anoxia induced by carbon monoxide It is as though the rhythmic discharge of the center resembled charges of gunpowder dropped on a hot surface, where, if the powder was dry, explosion was instant If, however, the powder making up the increments fed to the igniting surface was damp, then explosion would be delayed and the strength of the blast uncertain This is not a precise analogy with conditions in the respiratory center, but illustrates one of the ways in which the condition of the tissue may vary

Many influences dampen the respiratory center, so that, though breathing goes on, all margin of safety has been lost Drugs, such as morphine, dampen the breathing center The anesthetics are notable for their action in this fashion

The experiments utilized to illustrate this series of lectures have all been carried out under nembutal administered intravenously to dogs This compound is an extraordinarily useful anesthetic, from which the subject begins to recover immediately unless a dangerously large dose has been given All prolonged anesthesias by nembutal require, therefore, repeated intravenous injections of the drug Its effect on respiration is prompt If measurements of minute volume are made, there is an invariable and large reduction in the volume of breathing immediately fol

lowing the injection of anesthetic This reduction lasts ten to thirty minutes, being most intense if the animal's circulatory and respiratory conditions are poor After a little time, there is a return to a uniform and higher ventilation, but at each successive injection of anesthetic, the same reduction in breathing occurs This suppression of the breathing expresses a dampening of the respiratory center, a heightening of its threshold for the development and discharge of the volleys of nerve impulses which cause inspiration Medicine knows many drugs which act as central depressants of breathing, and very few which have more than a momentary opposite effect

It has seemed to me a very natural arrangement—in view of the conception that the respiratory center is excited to the point of discharging nerve impulses through the production of carbon dioxide by its own oxygen utilization—that chemoreceptors, bathed in the aortic and carotid blood and potently affected by anoxia, should be provided to augment the sensitivity of the respiratory center when anoxia is experienced At the same time, the enhancement of breathing resulting from anoxemia is never very great—far less than can easily be accomplished by inhaling carbon dioxide

But when it comes to depressing the respiratory center there is no agency so subtle, so common, and so persistently effective as lack of oxygen When a healthy man breathes air containing 8 per cent oxygen (3) his minute volume doubles or a little better The breathing follows no certain course, but eventually irregularity is apt to appear, and finally rapid shallow respiration, highly ineffectual for gas exchange in the lungs This last result was discussed in the preceding lecture, but you can see again what a vicious cycle anoxia provides Suppression of the efficiency of the respiratory center results in shallow breathing, which, in its turn, augments anoxemia, so that from every side oxygen lack steals in upon the victim

Let us look now at two experiments in which lung lymph was collected during the inhalation of oxygen poor mixtures The first of these is shown in Figure 21 (4) In this experiment the right lymphatic duct was cannulated in a dog under nembutal anes

thesia Arterial blood pressure was recorded and cardiac output measured under different experimental conditions In the first period, when room air was breathed, cardiac output at the end

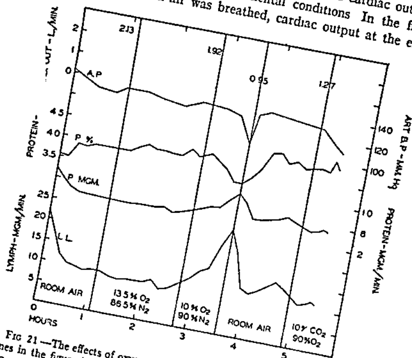


FIG 21 —The effects of oxygen lack on the flow of lung lymph The vertical lines in the figure block off periods of time during which air, 13 5 per cent oxygen etc were breathed. *L.L.*, lung lymph *P–MGM* protein in lung lymph in milligrams per minute *P %*, per cent of protein in lung lymph, *A.P.*, arterial blood pressure in millimeters of mercury Notice the abrupt increase in flow of lung lymph when 10 per cent oxygen and 90 per cent nitrogen are administered and the quick subsidence of flow when air is again supplied. (From Warren Peterson and Drinker (4), fig 3, p 647 By permission of the *American Journal of Physiology*)

of fifty three minutes was 2 13 l per minute Near the close of the second period, when 13 5 per cent oxygen in nitrogen had been breathed for eighty five minutes, cardiac output was 1 92 l per minute At the close of inhalation, during which 10 per cent

oxygen in nitrogen was breathed, output was 0 95 l per minut
This fall, it will be noted, was accompanied by a fall in arteri
blood pressure Final measurement of cardiac output, made forty
minutes following a return to air breathing, and when blood
pressure had recovered, gave a figure of 1 27 l per minute

At the outset lymph flow from the lungs decreased and then became quite steady The initial fall in lymph delivery in such an experiment is due to the fact that the duct is blocked for a time during cannulation This is followed by a high flow, due to emptying out of dammed up lymph

Notice, in Figure 21, that reduction of the oxygen breathed from the 21 per cent level in air to 13 5 per cent had no effect on lymph flow This reduction in oxygen did not cause the alveolar capillaries to leak abnormally But as soon as the oxygen was further reduced to 10 per cent, lymph production immediately rose, indicating that under these circumstances the lungs at once began to have to dispose of abnormal amounts of extravascular protein containing transudate The administration of 10 per cent oxygen was brief, fifty two minutes in all It was followed by shifting to air, not to pure oxygen Immediately the increased flow of lymph ceased, showing that the endothelium of the alveolar capillaries regained normal permeability at once

So favorable an immediate effect upon capillary permeability is not ordinarily secured, and will never be obtained if anoxia is at all protracted A more usual type of result is shown in a second experiment, pictured in Figure 22 In this experiment, after a considerable control period during which 100 per cent oxygen was given by inhalation, lymph flow fell promptly but did not return to normal during the ensuing ninety minutes

This result sums up my experience of the subtleties of alveolar capillary leakage due to anoxia It means, I believe, that if conditions of abnormal leakage continue until excess fluid has made any considerable entrance into alveoli and bronchioles, one can not expect prompt and complete relief from breathing oxygen This does not mean that the best resource for the treatment of pulmonary edema is not oxygen, but it does mean that the sooner

oxygen is given the greater the possibility of checking leakage from lung capillaries In the third lecture, I pointed out that oxygen will not prevent pressure stasis and atelectasis in the supine immobile patient, not because oxygen is not precisely the best agent to improve conditions in lung areas so affected, but because

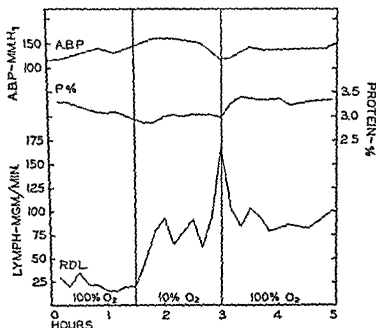


FIG 22—Another example of the effects of breathing an atmosphere low in oxygen on flow of lung lymph with an effort to restore normal conditions by breathing 100 per cent oxygen The vertical lines bound periods of breathing oxygen alone and low oxygen with nitrogen *R.D.L.*, flow of lymph from the right lymphatic duct *P* % protein in lung lymph in per cent *A.B.P* arterial blood pressure in millimeters of mercury

oxygen will not reach them unless something is done to clear the airways The same issue, but here much more serious, is at the back of the problem of treating lung edema when it has become a recognizable clinical entity Oxygen, however administered, cannot improve the condition of capillaries in a lobule it cannot

reach Its airway to the capillaries is effectively blocked by the fluid which is being steadily pushed into the alveoli, alveolar ducts, and bronchioles through which it must first pass

Two principles emerge from these experiments

1 Oxygen lack is the most potent and elusive cause of abnormal leakage from the lung capillaries and, as a consequence, administration of oxygen is the obvious method of treatment

2 If oxygen administration is withheld until the physician is sure pulmonary edema is present, then fluid will have reached many alveoli and bronchioles By this time, though high tensions of oxygen will be definitely useful, their utility will be far less than if given earlier, when the gas could really reach lobules everywhere in the lungs The lesson, never to be forgotten, is that if oxygen is to be most helpful, it must be used before the physician is sure it is needed

With the fact established beyond question that when transudation or exudation begins in the lungs oxygen is needed, then the real problem confronting the physician is not what he must give the patient, but how to give oxygen so that it will reach not only normal areas of the lungs but, in so far as possible abnormal lung tissue as well The problem of the cyanotic, distressed patient is usually appraised in terms of the general deprivation of oxygen which he so obviously exhibits But no real good can be accomplished by a slight alleviation of systemic anoxia if the fundamental state of the lungs is not improved at the same time The problem of giving an anoxic patient oxygen is thus one of wisely ordered technique, particularly a sagacious alertness for the early use of oxygen

I can remember very vividly my entrance into the partly finished Peter Bent Brigham Hospital in Boston as a frightened medical house officer That was in 1914, thirty years ago We were a more or less hand picked group of youngsters, brought together to undertake a new enterprise organized by Henry Christian alongside, and part of, the rejuvenated Harvard Medical School created by President Eliot We were there to examine the effects of new medical procedures, to try out the old ways of helping patients to

do all that could be thought helpful in the art of medicine But I am quite sure that neither as a house officer in this rather rarefied medical environment, nor some years later, when for a time I was chief resident in medicine, as well as acting head of the department of physiology in the Harvard Medical School, did I ever hear any one have the effrontery even to suggest that a patient be given oxygen to breathe!

I may be wrong, but it is my recollection that as precise immunological studies upon lobar pneumonia began, we commenced to examine these patients by physiological methods, and that the obvious oxygen lack which they exhibited at once received attention The result of this mounting interest was soon expressed in efforts to treat cyanotic patients by giving them oxygen to breathe If we had presumed to prescribe oxygen for anoxic patients in 1913, we would have been arrant quacks but by 1920 all sorts of methods were being tried for giving this gas to such patients

It is unnecessary for me to describe here the varied appliances and techniques used at the present time for giving oxygen Only recently Barach (5) published a short book in which current techniques for oxygen administration are described and illustrated To recapitulate all of this would be of no practical use The best that I can do is to indicate what seem to me to be defects in the ways oxygen is now given to patients and some of the directions in which inquiry should go in order to assure improvements

When oxygen therapy began in earnest, there was a conviction that the inhalation of oxygen in more than a 70 per cent concentration was dangerous, and this idea rested as a weight upon the problem of oxygen therapy for many years It has been known since the observations of Paul Bert that pure oxygen under high pressure will cause epileptiform convulsions This is an interesting but not important action of oxygen, since the oxygen pressures which produce convulsions are so extreme as not to be encountered except under the most unusual conditions On the other hand, there is no doubt that the continuous inhalation of 100 per cent oxygen at normal barometric pressure for six hours will cause irritation of the respiratory passages, a mild but progressive inflammation,

which fortunately is easily prevented In 1939, in an article on oxygen therapy, Boothby, Mayo, and Lovelace (6) described what they called administration of oxygen for forty eight hours, without the slightest adverse effects This statement of findings was undoubtedly correct for what actually occurred from these long administrations of oxygen They resulted in no damage But the oxygen was given through a mask, in itself somewhat leaky, and necessarily removed at times for coughing, feeding the taking of water, etc These interruptions are the saving grace in such so called "continuous administrations of oxygen" The fact is that if a man is placed in a chamber so that he inhales pure oxygen without a chance of interruption, he will eventually begin to experience the same sort of irritation of his respiratory tract as would come from a very mild dose of chlorine But the effect of high oxygen as an irritant is really a matter for small concern, since all evidence shows that if the rather feeble irritating action is interrupted from time to time it becomes of no consequence This is the reason why Boothby and his associates could administer 100 per cent oxygen through a mask without trouble for forty eight hours The exigencies of ordinary care of the patient interrupted the effects of pure oxygen as an irritant sufficiently to assure avoidance of this simplest expression of oxygen poisoning

Every therapeutic consideration directed toward the needs of the patient, calls for all the oxygen that can be delivered to the lungs The use of oxygen in medicine has failed to gain respect and confidence for two very simple reasons It is given inefficiently, and it is given too late

The first serious efforts at oxygen therapy were in terms of small rooms accommodating the patient in his bed and permitting ordinary nursing and medical care These installations were expensive, and their operation equally so Consequently, the oxygen chamber was reduced in size and became a tentlike contrivance enshrouding the bedridden patient wherever he might be Oxygen tents have given sick people much comfort They provide cool surroundings and an increase in the oxygen breathed but never

a certain and consistent supply of 100 per cent oxygen, which should be the aim in treatment

Naturally, also, since the beginning of its therapeutic use, oxygen has been given by means of masks In the early days almost anything sufficed for a mask I have watched house officers and nurses hopefully holding an ordinary funnel several inches above the face of a desperately ill patient, in the conviction they were supplying oxygen It was this sort of oxygen administration that made the use of an invaluable therapeutic aid practically a part of the last rites in hospital practice The house officer assembled whatever he could find for administration of oxygen, notified the church, and began to wonder what would be discovered at autopsy In recent years mask administration of oxygen has improved enormously, and the lessons of the war as to the absolute essentialness of nonleaky oxygen masks for high flying have taught many of us what can be done with such equipment Today the oxygen mask is the best way of giving oxygen It is inexpensive, and the patient really receives undiluted oxygen

In the ordinary employment of oxygen therapy, the physician waits, before resorting to the mask, until the patient is in desperate pass For such unfortunates, freedom from annoyance and rest are always imperative, and a mask over the mouth and nose is a final trial which often is given up on account of the patient's protests and those of his relatives Under such circumstances, an oxygen tent may be tolerated and may provide some relief, but the point I wish to make is that neither the mask nor the tent will win in these last ditch battles Oxygen given through a mask, a half hour on, then a rest, and then another period of inhalation, before the patient s lungs are so filled with transudate or exudate that oxygen cannot reach much of the lung tissue, may be a decisive factor in increasing the strength and resistance of the patient It is my opinion that we have been guilty of an unwise kindliness in our attitude toward oxygen therapy No one would delay operation upon a patient suffering from an acute and flourishing appendicitis because the sufferer objected to the preparations and to the prospects of a surgical operation But with oxygen we are irresolute

It is hard to believe that anoxia of dangerous extent impends, and that the chance to avoid this calamity is the immediate and persistent use of an oxygen mask

So far, in this discussion, we have thought only of giving a patient the benefit of all the oxygen possible by providing a non leaking mask so that 100 per cent oxygen reaches him steadily and at normal atmospheric pressure From the experiments described in this and preceding lectures, it should be clear that if high concentrations of oxygen reach the alveoli, the tendency for leakage from the lung capillaries due to anoxia will be checked In this demonstration, the fact is inherent that the higher the pressure of the oxygen in the air passages, the better the chance for oxygen to reach the blood in the lung capillaries, their lining endothelium, the smooth muscle cells, and all the varied cellular population of the lungs Recall a photomicrograph (Figure 11), shown in the second lecture, which made it clear that a layer of exudate or transudate thickens the barrier between the blood in the alveolar capillaries and the alveolar air We have been able to show, by recording flow of lymph from the lungs, that the production of thickened barriers of this sort between blood and lung air is checked if high concentrations of oxygen are inhaled before the situation has advanced too far, and before transudate or exudate has leaked into alveoli, to be moved up into bronchioles

If breathing pure oxygen under normal atmospheric pressure serves a useful end when the early stages of difficulty with gas transfer in the lungs are encountered, then increased pressure of oxygen in the alveolar air above the atmospheric level must be of further utility It has thus happened very naturally that in recent years patients needing oxygen have not only been given 100 per cent oxygen to breathe, but have been caused to breathe under some degree of positive pressure The simplest way to cause heightened oxygen pressure in the lung alveoli is to insert some block against expiration It has, however, been shown that resistance to expiration invariably induces enhanced inspiration, so that leakage from the lung capillaries is not checked to any useful degree But if pure oxygen is administered under higher than atmospheric

pressure and expiration is also to some degree blocked, then one may expect that oxygen will reach the endothelium of lung capillaries There will be pressure of oxygen into the pulmonary blood, and, finally, direct pressure against filtration of fluid from the capillaries into the interstitial tissues of the lungs and into the air passages

It is easy to agree to these physiological advantages, but not easy to contemplate afflicting a dyspneic patient with an oxygen mask or hood so arranged as to compel him to breathe against resistance In breathing, the active muscular event is inspiration It is an act in which man is constantly engaged, and for which he is thus always in training Resistance to inspiration, which is highly undesirable in pulmonary edema, can be tolerated quite well so far as the muscular act of getting air under difficulty is concerned, but when it becomes necessary to do active muscular work for each expiration, the load is less welcome We make oc casional violent exhalations in shouting in coughing in blowing into some of the larger and more offensive wind instruments, but we lack training for expiratory effort and object to a load upon this phase of breathing Since the physiological appropriateness of breathing against pressure—that is, inhaling oxygen supplied to a mask under more than atmospheric pressure and exhaling against this opposing load—is so well suited to check leakage from the lung capillaries, the problem to be settled is very practical We need to know what happens to normal persons and to those seri ously ill when made to breathe against pressure, and how much pressure can be employed Barach (7) has recently reviewed his own work and that of others in this field Apparently a normal adult can breathe without discomfort against a resistance of 6 cm of water, and patients with pulmonary edema from a variety of causes are able to meet the same load There seems justification for the belief that in irritative conditions, such for example, as follow the inhalation of chlorine or other irritating gases, the mucosa of the bronchioles tends to occlude these passages by swelling, and also that their smooth muscle may be thrown some degree of persistent contraction Both of these events

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V

ARTIFICIAL RESPIRATION

THE SUBJECT of artificial respiration has been confused and controversial through many years—a state of affairs which has arisen because of the idea that methods of artificial respiration very efficient in laboratory experiments or in the operating room are equally appropriate for field use in the common emergencies of drowning, electric shock, and gas poisoning The situations, however, are very different In the field emergencies, artificial respiration must be given at once and under diverse and unfavorable conditions, moreover, it must usually be applied by a layman In the laboratory or the operating room, mechanical appliances and experienced operators are available Unfortunately, however, many individuals whose position and authority have caused their pronouncements to have great weight have not distinguished clearly between the practical issues involved in these two very different situations

My interest in the problems of resuscitation and artificial respiration began in 1921, when I was asked by the American Gas Association to form a national committee to review the current methods for resuscitation in carbon monoxide poisoning, and if possible to suggest new treatment Such a committee was formed, and I was appointed chairman Its membership was a distinguished one Doctors Walter B Cannon, David L Edsall, Lawrence J Henderson, and Francis W Peabody, Professors, respectively, of Physiology, Clinical Medicine, Biological Chemistry, and Medicine at the Harvard Medical School, Yandell Henderson, Professor of Applied Physiology, and Howard W Haggard, Instructor in Applied Physiology, Yale University, Royd R Sayers, Chief Surgeon, United States Bureau of Mines, and Mr Charles B Scott, Bureau

4 WARREN, M F, PETERSON, D K, and DRINKER C K The effects of heightened negative pressure in the chest, together with further experiments upon anoxia in increasing the flow of lung lymph *Am J Physiol* 1942, **137**, 641

5 BARACH A L Principles and Practices of Inhalational Therapy J B Lippincott Company, Philadelphia London, and Montreal 1944

6 BOOTHBY, W M MAYO C W, and LOVELACE W R, II One hundred per cent oxygen Indications for its use and methods of its administration *J Am Med Assn*, 1939, **113**, 477

7 BARACH, A L The treatment of pulmonary edema due to gas poisoning in war and in civilian life with special reference to the use of positive pressure respiration *New England J Med*, 1944 **230**, 216

time The result has been a reasonable combination of field ex perience with a continuing interest in certain aspects of laboratory work upon breathing These facts are cited merely to indicate my acquaintance with the battlefield of artificial respiration—a field of debate on which I have watched lack of understanding and misunderstanding mix simple issues to a degree which has been unfortunate, though happily less consequential than has been con tended (3) for human life

Let us go back over the years to see something of the ways in which present problems have developed Owing to the fact that death in mammals is usually signalled by respiratory failure, with circulatory collapse following in a matter of minutes, to the laity the cessation of breathing has always meant death Naturally and from greatest antiquity there are reports of raising the dead, apparently miraculous revivals in which, as a matter of fact, merely something has been done to give the breathing a slight boost and so enable the victim to make another effort for himself

Emergency Artificial Respiration

When a man in good health suffers an accident which stops his breathing, the first and most fundamental issue which arises is how much time the rescuer may have before the circulation will also cease and death occur In Figure 23 (4), I have made what seems to me a fair diagrammatic appraisal of the situation This diagram makes it clear that fatal anoxia may often be warded off if artificial respiration is instituted during the first four minutes after breath ing stops, but that after this time the chances for recovery rapidly become chances indeed If the victim of respiratory failure is to recover, artificial respiration must be given without an instant of delay No method for ventilating the lungs, however ideal its proponents deem it, can stand against the rapid fall in the chances for survival so evident in the first five minutes of asphyxia Even the most enthusiastic supporters of mechanical devices for artificial respiration concur in this appraisal, and advocate, as the first measure to be used, some type of resuscitation method which any

of Safety, American Gas Association This committee was provided with funds to prosecute experimental and field work

After two years of deliberation and of experimental and field work, and after the publication of several researches and reports, the committee published a final report (1) of its findings The principal conclusions set forth in this report were that reliance upon mechanical devices for artificial respiration in acute emergencies was disastrous, that the lungmotor and pulmotor—then widely sold to lay organizations and to hospitals—were dangerous in terms of damage they might leave in the lungs, even if apparently successful in bringing about revival of breathing, that the prone pressure method of artificial respiration was the best for emergency use, and, finally, that the oxygen–carbon dioxide inhalation method for the treatment of carbon monoxide poisoning had the best promise for successful treatment of such emergencies

It is proper to point out that this committee financed the experiments of Henderson and Haggard (2) which resulted in the creation of portable inhalators for giving oxygen and carbon dioxide—devices entirely efficient and so safe as to make it desirable to place them in the hands of firemen, police squads, the employees of gas companies, or, in short, in the hands of any intelligent laymen whose duties might confront them with an emergency due to carbon monoxide poisoning

It should be made clear at this point that the committee under discussion did not indorse inhalators as mechanical instruments for giving artificial respiration, since this is precisely what the inhalators did not and could not accomplish Inhalators were, and are, a simple device, with but one substantial essential in their construction, namely, the provision of an unrestricted access to an oxygen–carbon dioxide mixture as the patient's breathing increases with carbon dioxide stimulation The patient, not the device, does the work of pulmonary inflation and deflation

Following the publication of the findings of the committee, I was asked to examine and comment upon methods of resuscitation then in use by municipal and utility company rescue squads in this country, and have continued such examinations up to the present

for the efficacy of the mouth to mouth maneuver While it is true that the oxygen in the expired air of the blower must certainly be higher than that available in the blood of the patient, and may be of some service on that account, the carbon dioxide in the blower's expired air can have little effect in stimulating the pa tient s respiratory center, since in respiratory failure the carbon dioxide of the blood in the lungs is so high that a 3 per cent in crease of this gas in the ventilating air would be of negligible consequence The real reasons for the efficacy of mouth to mouth insufflation reside to a considerable degree on reflex effects on the patient's breathing resulting from distension of his lungs by the insufflation maneuver Medical students, in their physiological studies of normal breathing, are invariably confused by the Hering Breuer reflex It is easy for them to understand that in the metabolism of the respiratory center carbon dioxide is produced, and that in a center normally supplied with oxygen and metabolizing normally, impulses bringing about inspiration result ing from carbon dioxide formation are discharged rhythmically But to understand further that nerve impulses from the lungs also have a marked influence upon breathing always causes difficulty Yet, it is fact that these reflex nervous effects from the pulmonary alveoli are not only of the utmost importance for normal breathing but are also of potential importance when breathing has stopped Divested of details, the facts of consequence are that if the pul monary alveoli are suddenly inflated to full or overfull capacity, volleys of nerve impulses, originating in vagal endings, reach the respiratory governing mechanism and bring about an expira tory effort—an effort which is followed by a correspondingly energetic inspiration Similarly, if an experimenter working with a normal animal instead of blowing into the lungs, sucks strongly so that alveoli are maximally collapsed, nerve impulses originating in the lungs bring about a strong inspiratory effort One can demonstrate the efficiency of these reflexes from the lungs for restoring breathing by inflating or deflating the lungs of an asphyxiated animal whose circulation is intact Either of these procedures results in an effort in the opposite direction, an effort

intelligent bystander can apply at once and without resort to mechanical appliances.

The most ancient method for restoring breathing is mouth to mouth insufflation—a method which, in my opinion, will always be one of the best At the present time, however, except for use on

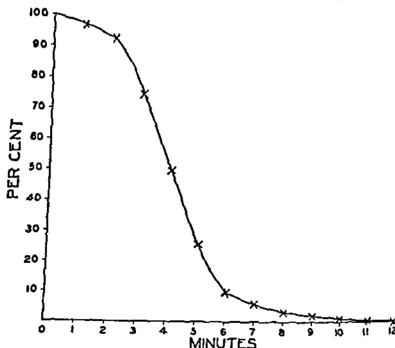


FIG 23—A diagram illustrating the chances of recovery in minutes of time after cessation of breathing, provided competent artificial respiration is given. *Abscissa*, time in minutes; *ordinates*, percentage chances of recovery (From Drinker (4), fig 1, page 287 By permission of the *Journal of the Oklahoma Medical Association*.)

stillborn infants, mouth to mouth insufflation has little vogue But the principles behind this simple maneuver have the best sort of physiological reasonableness Usually, it is assumed that the reason mouth to mouth insufflation works is because air containing a fair amount of oxygen and about 3 per cent of carbon dioxide is blown into the lungs This assumption is, however, not the real reason

for the efficacy of the mouth to mouth maneuver While it is true that the oxygen in the expired air of the blower must certainly be higher than that available in the blood of the patient, and may be of some service on that account, the carbon dioxide in the blower's expired air can have little effect in stimulating the patient's respiratory center, since in respiratory failure the carbon dioxide of the blood in the lungs is so high that a 3 per cent increase of this gas in the ventilating air would be of negligible consequence The real reasons for the efficacy of mouth to mouth insufflation reside to a considerable degree on reflex effects on the patient's breathing resulting from distension of his lungs by the insufflation maneuver Medical students, in their physiological studies of normal breathing, are invariably confused by the Hering Breuer reflex It is easy for them to understand that in the metabolism of the respiratory center carbon dioxide is produced, and that in a center normally supplied with oxygen and metabolizing normally, impulses bringing about inspiration resulting from carbon dioxide formation are discharged rhythmically But to understand further that nerve impulses from the lungs also have a marked influence upon breathing always causes difficulty Yet, it is fact that these reflex nervous effects from the pulmonary alveoli are not only of the utmost importance for normal breathing but are also of potential importance when breathing has stopped Divested of details, the facts of consequence are that if the pulmonary alveoli are suddenly inflated to full or overfull capacity, volleys of nerve impulses, originating in vagal endings, reach the respiratory governing mechanism and bring about an expiratory effort—an effort which is followed by a correspondingly energetic inspiration Similarly, if an experimenter working with a normal animal instead of blowing into the lungs, sucks strongly so that alveoli are maximally collapsed, nerve impulses originating in the lungs bring about a strong inspiratory effort One can demonstrate the efficiency of these reflexes from the lungs for restoring breathing by inflating or deflating the lungs of an asphyxiated animal whose circulation is intact Either of these procedures results in an effort in the opposite direction, an effort

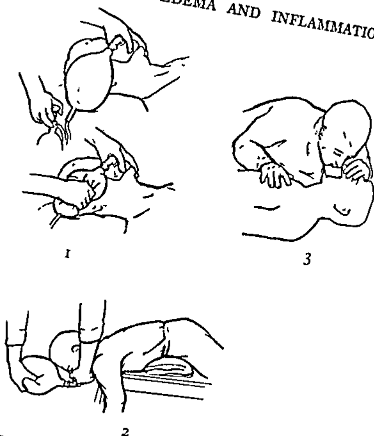


Fig 24—Simple methods for performing artificial respiration In *1*, the bag is filled with oxygen, and by squeezing it the operator forces the gas into the lungs When he is sure that the chest wall has expanded, he releases the bag, thus allowing expiration to take place. In *2*, the position used provides drainage from the lungs and throat In *3*, mouth to mouth insufflation is carried out, a layer of gauze being placed over the patient's mouth to prevent infection. Note the position of the right hand for determining the success of lung inflation (From Waters (5), figs 2, 3, and 5, pp 260–261 By permission of the *Journal of the American Medical Association*)

which, in its turn, may well be followed by further respiratory efforts.

The Hering-Breuer reflex mechanism, in terms of the vagal endings in the alveoli, is ruggedly resistant to anoxia, so that if

air or oxygen actually moves in and out of the alveoli the aid of these reflexes in starting normal breathing may be effective even when the circulation of the blood has practically stopped But emergency alveolar ventilation admits no delay, and if reflex stimulation of breathing is to be achieved real inflation of the ungs must be attained This is why mouth to mouth insufflation, a nethod seldom used for more than a few minutes and always with a eye to actual evidence of chest inflation, works effectively, and by such simple procedures as, for example, that illustrated by aters (5) (Figure 24), with the express stipulation that the erator must make sure that pressure on the oxygen-containing ber bag causes chest movement, are really effective [1] One can how unfortunately a blow and suck mechanical appliance, ad ed so that only minimal pressures can be reached before the machine reverses, may act in such a situation In reality, the use of lung inflation and deflation to stimulate breathing is a measure requiring medical judgment and experience, and cannot be left to an entirely automatic device such as the resuscitator

Two papers must be referred to in relation to these issues One of them, utilized by the Council on Physical Therapy of the American Medical Association (8) in their indorsement of blow and suck devices for the emergency treatment of suspended breath ing, is that of Martinez (7) from an obstetrical clinic in Pittsburgh This is an account of the successful use of the E & J resuscitator in causing 500 newborn infants to breathe normally The resuscita tors currently in use blow oxygen, or a mixture of oxygen and carbon dioxide or air, into a mask covering the mouth and nose of the patient, and for expiration suck it out again One can easily see that such an appliance, ready for use in the delivery room of a modern hospital, may perform creditably, particularly if in the hands of a well trained physician who does not expect too much from it But to apply the results of Martinez's findings to the problem of resuscitating a drowning victim on a bathing beach, a

[1] For a further clinical discussion of these issues see a very recent paper by Alfred D Biggs (6) This paper is a refreshing physiological antidote for the sweeping assertions found in the article by Martinez (7)

man shocked by electricity, or a patient suffering from the more subtle effects of carbon monoxide, is obviously nothing more than hopeful thinking The second and much more interesting paper is that of Thompson and Birnbaum (9) These investigators found that if dogs had ceased to breathe they could be revived by blowing nitrogen into their lungs and then sucking it out for expiration This work is a convincing laboratory demonstration of the efficacy of the Hering Breuer reflexes for causing spontaneous efforts to breathe But, again, the fact it teaches does not apply to the usual field experience requiring artificial respiration The only sort of blow and suck agency certainly available for use in emergencies requiring instant employment of resuscitative measures is mouth to mouth insufflation, a noncommercial instrumentality with a history which loses itself in the past

From the point of view of an inquiry such as this, artificial respiration must fit a number of needs

1 The principal aim of the method used may be the promptest possible stimulation of normal respiratory movements For this purpose the best line of attack is through the Hering Breuer reflexes, in the hope that alveolar inflation or deflation will be followed by brief respiratory activity For sustained breathing carbon dioxide stimulation, accompanied by high concentrations of oxygen, is the soundest reliance

2 A satisfactory method of resuscitation must, from the outset, provide such a degree of ventilation as to relieve the patient immediately from the dangers of oxygen lack, so that the circulation will continue unimpaired This is the accomplishment of the ordinary types of artificial respiration which merely aim to give the patient time to recover his natural ability to breathe The claims that blow and suck devices aid the circulation are not based upon sound observation (10)

3 Finally, and this is the subject of the second large section of this chapter, artificial respiration is often required for hours even years, and the type employed must, of itself, do no harm to the patient

The second and third of these requirements of a satisfactory

method of artificial respiration are in reality rather separate from the first, though, as I have pointed out, this distinction has usually been overlooked All of us agree that if a patient is not breathing, anything that will start respiratory movements is permissible But this by no means gives carte blanche to continuous use of methods of artificial respiration, which, if carried on for even an hour, will of themselves not only gradually fail to ventilate the lungs but may also leave substantial damage in their wake It being understood that inflation and deflation of the alveoli is a stimulus to breathing, even though brought about by positive pressure and suction instead of in the normal manner, the problem which confronts us is the simplest way to accomplish this end Martinez s evidence, based upon the use of the E & J resuscitator in a large series of infants, shows that an elaborate appliance apparently meets the simple and very temporary utility of stimulating breathing through the Hering Breuer reflexes This should not be interpreted as evidence that the appliance is particularly efficient and does no damage to the lungs if continued in use for an hour or more It is an expression of the fact that the resuscitators in specially trained medical hands, as Martinez is careful to point out, may perform the task of expanding and contracting the lung alveoli for the very brief period in which this stimulation of the respiratory center is useful

But consider how simply competent anesthetists have achieved the same result over many years Waters (5) has illustrated a technique used widely in operating room emergencies This procedure is shown in Figure 24 Here the anesthetist utilizes a rubber bag filled with oxygen and connected to a face mask as his means of positive pressure inflation of the lungs, or, the oxygen filled bag being unavailable, elicits the Hering Breuer reflex effects by mouth to mouth insufflation This procedure has been used by anesthetists for years and operates effectively and without the expense of elaborate apparatus whose mechanical attractiveness far outweighs its true usefulness If physicians desire mechanical devices equipped with valves so that artificial respiration may be given by a positive blast through a face mask or nasopharyngeal

not comparable to what might happen in prone and u
patients

British experience has supplied substantial indorseme
instances in which the simple prone pressure procedu
sulted in spontaneous breathing and complete recovery
twelve hours In 1933, Sir William Bragg (12) was conf
the case of a friend suffering from progressive muscula
and eventually so weak that both the patient and his a
had become exhausted and desperate with efforts at
respiration by manual methods Bragg bound a football
upon the lower part of the patient's chest and abdomen,
it through a tube to a second bladder, which could be co
and released by a hinged board above the motivating blad
arrangement worked immediately, and was soon transl
the Bragg Paul pulsator shown in Figure 25 This figure
patient in a bed receiving artificial respiration by me
mechanical pulsator An inextensible binder about the up
of the abdomen and lower part of the chest of this patient
and restrains a distensible element activated for distens
collapse by an electrically operated pump in the box at th
the patient With the help of such a machine, Sir William
lived for three years, and the device has subsequently b
use in England as an instrument for supplying breathin
many conditions and over long periods of time So far as
been able to learn, there has been no comment unfavorabl
procedure in terms of damage to the lungs occasioned b
effect, a testimonial to the lack of lung injury from t
methods of artificial respiration

Of greater practical importance than the Bragg pulsato
procedure for artificial respiration suggested by Eve (13) i
It happened that this British physician was confronted by what
become an unusual emergency, a child with
paralysis of breathing The child, two years old, was dy
clear its respiratory passages o ve held the
head down and noticed that th
duced expiration—an

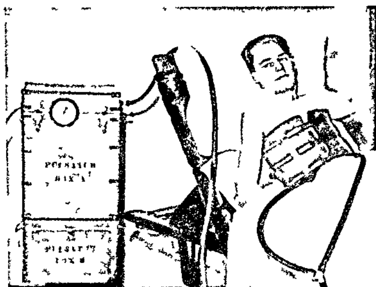
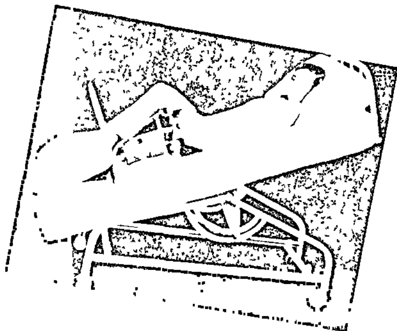


Fig 25.—The Bragg Paul pulsator in operation upon a patient The boxes contain a pump motor and accessories to drive air into rubberized bag held under the broad belt Inflation compresses the lower part of the chest and upper abdomen causing expiration Inspiration follows as a result of the elastic recoil of the parts (From Report of the Respirators (Poliomyelitis) Committee Special Report Series No 237 Medical Research Council London 1939 Breathing Machines and Their Use in Treatment Plate III fig A facing p 15 By permission of the Controller of His Britannic Majesty's Stationery Office)



convincing character cannot be carried out upon men unless they have actually stopped breathing, these investigators used dogs in their experiments, and brought about cessation of breathing by transection of the spinal cord just below the first cervical vertebra or by excessive doses of nembutal They measured the oxygen content of arterial and venous blood, the cardiac output, and the minute volume of breathing during artificial respiration induced by a laboratory pumping device adjusted to give the animal a minute volume of normal value, during artificial respiration by the Schäfer method as well as it can be given to a dog, and, finally, during artificial respiration with the tilting method advocated by Eve The comparative figures are of little practical significance since blow and suck artificial respiration through a tracheal cannula under the usual laboratory surroundings is always efficient for a time Similarly, what one can do with a dog in the way of pressure artificial respiration by simulated Schafer technique is in no sense comparable to what might perhaps be achieved with man On the other hand, there is little apparent reason to feel that the tilting method applied to a dog unable to breathe may not give results reasonably comparable to what one might expect to gain in a human case The important facts of Hemingway and Neil s experiments are that the rocking method gave excellent arterial saturation with oxygen sustained cardiac output at a good level, and provided a very respectable tidal volume of breathing One significant point brought out in this interesting paper is the extent of cardiac filling achieved by the rhythmic head down position If, with this aid to the circulation, sufficient ventilation was secured to prevent anoxia of the heart, the animal was safe—indeed quite normal for his physically inactive condition Hemingway and Neil's series of experiments did not include any observations upon possible damage to the lungs assessed at the close of the observations or, in nembutal experiments, a day or two after the animals had recovered The experiments are, however, straightforward evidence that in the emergency of respiratory failure Eve's rocking method, started as soon as possible after breathing stops, provides very efficient ventilation The authors conclude

their paper with the admonition that, in the practical employment of the method, operators must always be instructed to use the Schafer prone pressure method until even the crude arrangements necessary for Eve's method can be brought together

From the time of John Hunter (17), artificial respiration by means of a pump, connected in varying ways with the air passages so as to blow air into the lungs for inspiration and suck it out for expiration, has had great appeal to every one interested in the resuscitation problem Physiologists have tied a cannula in the trachea, connected it with an air pump, and given artificial respiration in a great variety of physiological experiments many of which have resulted in fundamental information It must, however, be realized that no physiologist using artificial respiration in a mammalian experiment employs a pump with a blow-off valve arbitrarily set so that, no matter what the needs of the animal as regards oxygenation of the blood, the supply is determined by an unalterable setting of the pump One cannot quarrel with the wisdom of providing for safe pressures in appliances freely sold to and used by nonmedical personnel—as is the case with the resuscitators now in use, and was the case with the final pulmotor, prototype of the resuscitators The physiologist giving artificial respiration by such a device changes the setting of his pump as his observations indicate necessary He employs the lungs to aerate the blood, and, since his experiments under such circumstances are ordinarily terminated by sacrificing the animal, he is unconcerned about the condition in which the method of ventilation leaves the lungs at the close of the experiment

In spite of the potential hazards of such a procedure, the mechanical attractiveness of substituting blow and suck breathing for the normal negative pressure breathing has led to many efforts to create a pumping device to provide artificial respiration It is significant that no such appliance has been devised or seriously advocated by a clinician accomplished in respiratory physiology or by a physiologist since the time of John Hunter Yet the medical profession has for years had incessant sales onslaughts by ingenious mechanical engineers who have devised appliances which are

tion over long periods of time if the patient is not too paralyzed to cooperate If he loses control of swallowing—that is, if he becomes a case of generalized bulbar paralysis—then factors enter the problem beyond the issues of simple artificial breathing The respirator has taught us a good deal about the inexorableness of ascending paralytic respiratory failure

From the physiological point of view, one very interesting problem about the respirator seems to me to be the fact that no one has been able to make one of the cuirass type, as shown in Figure 27, which works well unless the patient can, to some extent breathe *for himself I have pointed out (4) that the difficulty with* cuirass respirators may be due to the abdominal pressure caused by the seal which surrounds the abdomen just above the iliac crests—pressure which may impose a block to diaphragmatic movement This is, however, merely a suggestion for which I can supply no investigative support The difficulty of inflating the lungs of premature infants is not answered by the comparatively mild ministrations of the respirator If anything beyond the natural abilities of the infant can accomplish this, it is positive pressure ventilation alone—given for a few minutes only

Finally, in view of recent attention to it (19), a further device for supplying respiration must be mentioned In 1924, Thunberg (20) made what he called a barospirator This machine was the result of an interesting application of physical principles *to* breathing In Thunberg s appliance, the subject—in 1927, I myself had the interesting experience of being a subject—is inclosed in a metal cylinder which is sealed tight, except for an adjustable *cock at the top and connection with a large capacity* pump for rhythmically making and reducing pressure in the cylinder inclosing the patient The way in which the barospirator works is easy to demonstrate If one places a lighted candle inside a moderate sized conical glass flask on the laboratory table the candle may flicker and go out If, in the same flask, the candle is placed within the barospirator, in which alternating positive and negative pressure is experienced the flame never fades Yet the glass flask has necessarily remained unchanged during the experi

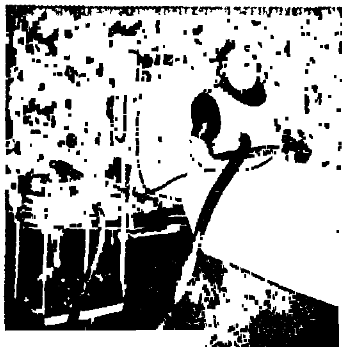


Fig 27—London County Council cuirass respirator (From Report of the Respirators (Poliomyelitis) Committee Special Report Series No 237 Medical Research Council London 1939 Breathing Machines" and Their Use in Treatment Plate IV fig A facing p 16 By permission of the Controller of His Britannic Majesty's Stationery Office and of the London County Council

ment Thunberg substituted pressure change for volume change in the fundamental gas law vp = v'p Normal breathing is volume breathing, accomplished by expanding the chest for inspiration, thus making room for more air under normal atmospheric pressure At expiration, the thoracic size is reduced In pressure breathing, variations in pressure above and below atmospheric level are applied to the outside of the body and into the air passages simultaneously The same conditions are involved in the experiment with the candle in the flask No change can occur in the size of the flask, and the oxygen supply which keeps the flame alight is provided by the variations in pressure The experiment is of more than theoretical interest, since when a man is placed in a barospirator and variations in pressure of sufficient size are applied, spontaneous breathing stops, and the subject lies perfectly still without realizing that respiratory movements have ceased Thunberg's clinical associates in Sweden treated a number of patients in a barospirator large enough to accommodate a physician nurse, and patient The results in these acute instances of respiratory failure were not striking It is, however, possible that, with present day knowledge of the localizing effects of lung quiescence on pulmonary infections, therapeutic use may be made of Thunberg's method Certainly animal experiments in which breathing movements are suspended for some days would be of decided interest and value

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CONCLUSION

At the close of this presentation of so old a subject as pulmonary edema, it is fitting to point out some of the things which should have been included in such a discussion, but which I have not attempted to treat since I lack clinical or experimental acquaintance with them.

Pulmonary edema sometimes occurs very abruptly and under circumstances which make changes in the permeability of the lung capillaries due to toxins or unfavorable pressures in these vessels improbable as initial causes. There is, for example, a large literature upon neurogenic pulmonary edema. In edemas of this sort, leakage of fluid into the lungs occurs so rapidly and so unexpectedly that it appears as if something must suddenly pull a trigger bringing about the edema, which, once started, proceeds along the lines discussed in these lectures. Upon what the initiation of edema in such cases depends, I can express no opinion. But once established, the consequences of the edema are identical with those involved in transudation from less intricate causes. In these lectures, however, the general thesis which I have wished to present is not an over all picture of the causes of pulmonary edema. It is, rather, the part played in its causation by changes in the permeability of the lung capillary endothelium, and particularly the part played by anoxia in effecting these changes.

To this end, the first lecture is devoted to an exposition of the anatomy of the lungs as it relates to the problems of transudation. The capillary circulation of the lungs is shown to be a close-meshed net surrounding the alveoli, a net so extensive that the blood showers over the alveoli in what amounts to a continuous sheet. This vast capillary area is large enough to meet the most extreme conditions provided by the heaviest physical exercise. This fact, however, imposes the possibility that a man at rest may

dispense with a great part of the capillary area, since he can accomplish his respiratory needs through a comparatively small section of the lungs

The first lecture also points out that the lung capillary endothelium depends for its oxygen supply upon the air reaching the individual alveoli, and not—as is the case in the rest of the body—upon oxygen brought by the arterial blood It thus happens that when transudates and exudates, leaking into the alveoli and forced up into the bronchioles, exclude air from groups of alveoli anoxia results, with its inevitable effects on capillary permeability Exudates or transudates in the lungs depend to a certain extent upon the lymphatics for removal In the lungs the lymphatic system is extraordinarily extensive, consisting of a vast network of vessels which drain via the right lymphatic duct into the right subclavian vein This duct is, however, very small, and constitutes a veritable bottleneck in the pathway of lymph drainage from the lungs

The first lecture continues with a correlation of the deceptive possibilities of lung function at different grades of respiratory need with the existence in the lungs of large amounts of smooth muscle and of elastic tissue—which, it is suggested, enable the lungs to adapt their size to changing respiratory requirements

In the second lecture, the balance of forces regulating movement of water through the walls of typical systemic capillaries is contrasted with the novel conditions found in the lungs These novel conditions are an insignificant pulmonary arteriolar circulation, which provides little opportunity for conventional vasomotor regulation, an enormously large network of capillaries, a low capillary blood pressure, and, finally, a variable degree of negative pressure in the thorax, which acts toward drawing water out of the pulmonary blood stream

On the basis of this setting in the lungs, the effects are discussed of alterations in the permeability of the capillary walls, particularly those due to anoxia, and the peculiar situation of the lung vessels is pictured in its relation to the occurrence of anoxia. Finally—though lymphatics all over the rest of the body have as

their principle function the restoration of blood proteins from the interstitial tissues to the blood vessels—the inefficiency of the lung lymphatics in removing excessive transudation is made clear by a description of the results of employing a novel experimental agent This compound, though it has no effect on capillaries in other parts of the body, by increasing the permeability of the lung capillaries causes fatal pulmonary edema with pleural effusion

In the third and fourth lectures, these physiological analyses become the basis, first, of a discussion of the effects of breathing on transudation, and, second, of the treatment to be applied when excessive transudation is imminent or is occurring From the physiological point of view there are two lines of therapeutic attack upon pulmonary edema first, to combat the progressive effects of anoxia in causing undue capillary leakage, and, second, to modify intrapulmonary pressure conditions so as to resist the tendency of the normal negative pressure in the chest to increase the flow of water out of the lung capillaries

The final section of the monograph, on artificial respiration, has been added because of my conviction that many of the matters discussed in the preceding lectures need to be clarified for all of us who are concerned with arresting the fatal anoxia of suspended breathing I have attempted to point out in very short space that three things must be considered in connection with artificial respiration first, the efficacy of the method in supplying oxygen second, the possible effects of the method in renewing the normal activity of the respiratory center, and third, the effects of the method used on the lungs This last aspect of the problem of artificial respiration has received too little attention from those concerned with the problems of resuscitation In the past, if a patient who has stopped breathing has regained power to breathe, we have deemed the resuscitation measures used successful But perhaps if we realize that, at the same time, the measures used may have left the patient a legacy of abnormalities in the lungs, which a more wisely conceived technique would have avoided our conceptions of "successful resuscitation" may be somewhat modified Since it has been impossible to discuss all of the great number

of procedures available for combating respiratory failure, I have arbitrarily selected for discussion those methods which best illustrate what I believe to be the really important underlying principles

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